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■

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

[4110-03-M]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 76N-0400]

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The agency is issuing final regulations regarding good laboratory practice in the conduct of nonclinical laboratory studies. The action is based on investigatory findings by the agency that some studies submitted in support of the safety of regulated products have not been conducted in accord with acceptable practice, and that accordingly data from such studies have not always been of a quality and integrity to assure product safety in accord with the Federal Food, Drug, and Cosmetic Act and other applicable laws. Conformity with these rules is intended to assure the high quality of nonclinical laboratory testing required to evaluate the safety of regulated products.

EFFECTIVE DATE: June 20, 1979.

FOR FURTHER INFORMATION CONTACT:

Paul D. Lepore, Bureau of Veterinary Medicine (HFV-102), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, (301-443-4313).

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) is establishing regulations in a new Part 58 (proposed as Part 3e) in Title 21 (21 CFR Part 58) regarding good laboratory practice. These constitute the first of a series of regulations concerning investigational requirements which are being developed as a result of the FDA Bioresearch Monitoring Program. Proposed regulations, providing interested persons 120 days to submit comments, were published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206). In addition, public hearings were held on February 15 and 16, 1977 for the presentation of oral testimony on the proposal. Twenty-two oral presentations were given (transcripts are on file with the Hearing Clerk, Food and Drug Administration), and 174 written comments were received. The comments have been categorized and include the following: manufacturers of regulated products (64), associations (40), medical centers (20), private testing or consulting laboratories (18), educational institutions (15), government agencies (8), individuals (8), and an airport director (1).

In the proposal, regulations were designated as a new Part 3e. This final rule incorporates them into a new Part 58 (21 CFR Part 58). The following redesignation table correlates the new sections with those proposed, and, in most instances, reference to the new sections will be used hereinafter.

New Section	*Old Section*
Subpart A	
58.1	3e.1
58.3	3e.3
58.10	3e.10
58.15	3e.15
Subpart B	
58.29	3e.29
58.31	.....
58.33	3e.31
58.35	3e.33
Subpart C	
58.41	3e.41
58.43	3e.43
58.45	3e.45
58.47	3e.47
58.49	3e.49
58.51	3e.51
58.53	3e.53
Subpart D	
58.61	3e.61
58.63	3e.63
Subpart E	
58.81	3e.81
58.83	3e.83
58.90	3e.90
Subpart F	
58.105	3e.105
58.107	3e.107
58.113	3e.113
Deleted	3e.115
Subpart G	
58.120	3e.120
58.130	3e.130
Subpart J	
58.185	3e.185
58.190	3e.190
58.195	3e.195
Subpart K	
58.200	3e.200
58.202	3e.202
58.204	3e.204
58.206	3e.206
58.210	3e.210
58.213	3e.213
58.215	3e.215
58.217	3e.217
58.219	3e.219

As a part of the overall bioresearch monitoring program that was described in the proposal, a pilot inspection program was carried out to assess the current status of laboratory practice of nonclinical testing facilities to aid in evaluating the relevance of the proposed regulations, and to identify any unanticipated difficulties in implementing an agency-wide monitoring and compliance program for the testing facilities.

The pilot inspection program began in December of 1976 and covered a representative sample of testing facilities. The results of these inspections have been evaluated, and the results of the analysis have been made available to the public as OPE Study 42, "Results of the Nonclinical Toxicology Laboratory Good Laboratory Practices Pilot Compliance Program." Notice of availability of this report was published in the FEDERAL REGISTER of October 28, 1977 (42 FR 56799).

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GENERAL ISSUES

1. Many of the written responses to the proposal were in two parts: a discussion of broad issues and a critique of the regulations by section and paragraph. Over a thousand individual items have been considered.

2. Thirty-two comments requested republication of the proposed regulations as guidelines.

The Commissioner of Food and Drugs advises that publishing guidelines rather than regulations was considered and rejected before publication of the proposal. The question was considered again in preparation of this order, and again rejected. The seriousness of problems encountered in testing facilities demands the use of an approach that will achieve compliance directly and promptly. Only by specifying the requirements for compliance in detailed, enforceable regulations can the Commissioner be assured of the quality and integrity of the data submitted to the agency in support of an application for a research or marketing permit.

3. Some comments objected to the incorporation by reference of other laws, recommendations, and guidelines as being either redundant or without the authority conferred by rulemaking procedures as required by the Administrative Procedure Act. It was also asserted that such incorporation could lead to confusion.

The Commissioner agrees that these regulations should not duplicate regulations and requirements subject to the purview of other agencies. Therefore, reference to animal care provisions of the Animal Welfare Act of 1970 (Pub. L. 91-570) and recommendations contained in Department of Health, Education, and Welfare (HEW) Publication No. (NIH) 74-23 have been deleted from §§ 58.43(a) and 58.90(a) (21 CFR 58.43(a) and 58.90(a)). Also, all provisions that referred to regulations of the Occupational Safety and Health Administration or were concerned with the health and safety of employees have been revised or deleted, i.e., 21 CFR 58.33(a) (by deletion of proposed 21 CFR 3e.31(a)(11)), 21 CFR 58.53(b), 21 CFR 58.81 (by deletion of proposed 21 CFR 3e.81(b)(10)), and 21 CFR 58.120(a) (by deletion of proposed 21 CFR 3e.120(a)(17)). Reference to the regulations of the Nuclear Regulatory Commission has been removed from § 58.49; and proposed § 3e.115, dealing with the handling of carcinogenic substances, has been deleted. In addition, the Commissioner has deleted reference to the various animal care guideline cited in the proposal.

4. Some comments said the regulations should not be retroactive to previous studies or those ongoing and should include reasonable transitional provisions for their implementation.

To give nonclinical laboratory facilities adequate time to implement required changes in their organization and physical plant, a period of 180 days after publication in the FEDERAL REGISTER is provided for these regulations to become fully effective. The regulations are not retroactive. All studies initiated after the effective date shall be subject to the regulations. The remaining portions of studies in progress on the effective date of the regulations shall be conducted in accordance with these regulations.

5. A number of comments challenged the general legal authority of FDA to issue good laboratory practice regulations. Other comments challenged the legal authority to require record retention or quality assurance units, or to specify the content of required records or location of storage.

The Commissioner finds that the authority cited in the preamble to the proposal (41 FR 51219; Nov. 19, 1976) provides a sound legal basis for the regulations. Although many matters covered in these regulations are not explicitly mentioned in any of the laws administered by the Commissioner, the Supreme Court has recognized, in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973), that FDA has authority that "is implicit in the regulatory scheme, not spelled out *in haec verba*" in the statute. As stated in *Morrow* v. *Clayton*; 326 F.2d 36, 44 (10th Cir. 1963):

> However, it is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning* v. *Family Publications Service, Inc.*, 411 U.S. 356 (1973); see also *National Petroleum Refiners Association* v. *F.T.C.*, 482 F.2d 672 (D.C. Cir. 1973). The Commissioner concludes that there is ample authority for the promulgation of good laboratory practice regulations. No comment presented any explanation or information to the contrary, let alone a cogent argument that FDA lacks legal authority under existing statutes. The standards prescribed represent amplification of the legal requirements regarding evidence of safety necessary to approve an application for a research or marketing permit and parallel, to a great extent, steps that FDA has found have been taken by members of the regulated industry to improve nonclinical laboratory operations.

6. One comment argued that the opinion of the Court of Appeals in *American Pharmaceutical Association* v. *Weinberger*, 530 F.2d 1054 (D.C. Cir. 1976), should be read to limit FDA's authority to issue regulations under section 701(a) of the act (21 U.S.C. 371(a)).

The Commissioner disagrees with the argument advanced in the comment. As discussed in the preamble to the proposed regulation, the agency's authority to issue regulations under section 701(a) of the act has been upheld by the courts. (See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *National Confectioners Association* v. *Califano*, No. 76-1617 (D.C. Cir. Jan. 20, 1978); *Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).) The question is not FDA's authority to issue regulations under section 701(a) of the act per se, but whether regulations issued under section 701(a) of the act appropriately implement other sec-

tions of the act. As articulated in the original proposal, and as discussed in the previous two paragraphs, the Commissioner has determined that these regulations are essential to enforcement of the agency's responsibilities under sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act, as well as the responsibilities of FDA under sections 351 and 354-360F of the Public Health Service Act.

7. A number of comments said various sections of the act did not specify the submission of safety data or did not deal with "applications for research or marketing permits."

The Commissioner has reviewed the comments and finds that the comments are based on a misunderstanding of the phrase, "applications for research or marketing permits." This concept is discussed in relation to § 58.3(e) below. Each cited provision contains authority for FDA either to require submission of, or to use, nonclinical safety data to justify a decision to approve the distribution of a regulated product.

8. A number of comments said the cost of implementing the proposed regulations would be prohibitive to smaller testing laboratories and would, at the least, result in a substantial increase in the cost of product testing.

The Commissioner agrees that implementation of these regulations will increase the cost of nonclinical laboratory testing. The Commissioner finds, however, that such costs are justified on the basis of the resultant increase in the assurance of the quality and integrity of the safety data submitted to the agency. The agency has previously concluded (see the FEDERAL REGISTER of November 19, 1976 (41 FR 51220)) that this document does not contain regulations requiring preparation of an inflation impact statement under Executive Orders 11821 and 11929, Office of Management and Budget Circular A-107 and the guidelines issued by the Department of Health, Education, and Welfare. For a notice on the availability of the agency's economic impact assessment regarding rules for good laboratory practice for nonclinical laboratory studies, see the FEDERAL REGISTER of February 7, 1978 (43 FR 5071). The revisions in this final rule, along with the findings of the pilot program, which showed that many of the inspected facilities were already substantially in compliance with the proposed regulations, should allay some of the concerns of small facilities regarding cost or feasibility of compliance.

9. Many comments suggested changes in language, grammar, terminology, punctuation; sentence structure, and other editorial changes to clarify or improve upon the requirements as stated in the regulations or to eliminate redundancies or inconsistencies. Comments that raised significant policy questions, suggested changes in the substance of the regulation, or otherwise required, in the Commissioner's opinion, a specific response, are discussed individually below. Many of the suggested changes, however, were editorial and stylistic and do not warrant a detailed discussion.

The Commissioner has reviewed each of these numerous editorial and language changes to determine whether it offered an improvement in clarity or definition, eliminated an obvious error or redundancy, promoted consistency with other portions of the regulations, or otherwise identified textual problems that had not been previously noted by FDA. Where the proposed alternative language or other changes suggested by the comments were superior to the proposal, they were adopted in substance or verbatim. Where they did not offer any improvement, the Commissioner declined to accept them.

GENERAL PROVISIONS

SCOPE

10. Numerous comments addressed the stated scope of the proposed regulations (§ 58.1). Six comments said the proposed scope was vague. Ten comments said the scope should be limited to long-term animal toxicity studies. Twenty-two comments indicated that the scope should be limited to animal safety studies to be submitted to FDA. Individual comments recommended limiting the scope to studies performed on marketed products, studies performed on animals and other biological test systems, or studies submitted in support of a color additive petition, food additive petition, investigational new drug application, new drug application, or new animal drug application.

In the preamble to the proposed regulations, the Commissioner set forth the reasons for the broad terminology employed in the statement of scope, stating "these regulations are intended to ensure, as far as possible, the quality and integrity of test data that are submitted to FDA and become the basis for regulatory decisions made by the Agency." In the proposed rule (41 FR 51210), the Commissioner specifically invited comments on which laboratories and/or studies should be subject to the regulations, and further, on whether the scope of the regulations should be defined in terms of the type of testing facility rather than the type of study performed. Based on the review of the comments, the Commissioner has chosen to describe the scope of the regulations in language that is only slightly changed from the proposal. Further clarification of scope is achieved by the specific definition of the key terms, "nonclinical laboratory study" and "application for research or marketing permit" in § 58.3. Taken together, these provisions eliminate any vagueness in the scope of these regulations.

The Commissioner has rejected the request to narrow the scope by listing in the regulation specific types of studies covered. Any such list, if it included all types of studies used by the agency to assess the safety of all the products it regulates, would be cumbersome and might exclude specific types of studies that could become important to future safety decisions. The Commissioner emphasizes that this decision does not mean, however, that the scope of the regulations is unlimited. The scope of the GLP regulations is limited in several ways.

First, they apply only to nonclinical laboratory studies that are submitted or are conducted for submission to the agency in support of a research or marketing permit for a regulated product. Language has been added that provides that the scope includes studies "intended" to support applications for research or marketing permits. This language was included in the preamble to the proposed regulation (41 FR 51209), and the Commissioner has added the language to the regulation because it helps to make clear in advance when a study should comply with the regulation and when a study should be listed on a testing facility's master schedule sheet as a nonclinical laboratory study subject to these regulations (§ 58.35(b)(1)). Tests never intended to be submitted to the agency in support of (i.e., as the basis for) the approval of a research or marketing permit, such as exploratory safety studies and range-finding experiments, are not included even though they may be required to be submitted as part of an application or petition.

Second, the definition of "nonclinical laboratory study" (§ 58.3(d)) makes it very clear that studies utilizing human subjects, clinical studies, or field trials in animals are not included.

Third, the scope of coverage is now limited to safety studies, i.e., those which can be used to predict adverse effects of, and to establish safe use characteristics for, a regulated product. "Functionality studies" have been excluded in the final rule.

Fourth, the definition of "test system" (§ 58.3(i)) taken together with the definition of "nonclinical laboratory study" makes it clear that the scope of coverage is confined to studies performed on animals, plants, microorganisms or subparts thereof.

Products regulated by the agency, for which safety data may be required,

cover a wide range of diverse items that pose quite different types of risk. Examples include implantable medical devices; indirect food additives which may occur in food in very small quantities; direct food additives which may be consumed on a daily basis in larger quantities; human drugs intended for prescription or over-the-counter use; animal drugs intended for use in pets and other companion animals of social importance, drugs used in food-producing animals (drug residues can become a part of food); radiation products used in the diagnosis and/or treatment of a disease or condition; radiation products (e.g., microwave ovens and television sets) widely used by the public; vaccines; and blood components and derivatives.

The guarantee of the safety of each of these product classes requires conducting a broad spectrum of safety tests, all of which should be subject to the same standards. Therefore, the Commissioner rejects the proposal to limit the scope of these regulations to long-term animal toxicity studies. Median lethal dose (LD_{50}) and other short-term tests are covered by the regulations because they may serve as part of the basis for approval of, for example, use of an indirect food additive or an investigational new drug in man.

In vitro biological tests are included insofar as such tests have a bearing on product safety, even though they are not now used in agency decisions, because they may in the future become important indicators of safety. Examples of such tests include short-term mutagenicity tests as well as various other tissue culture and organ tests.

Also included in the scope of these regulations are studies of safety of regulated products on target animals, acute toxicity studies on a final product formulation, studies of test articles that are completed in 14 days or less, studies conducted on test articles used in "minor food producing species of animals," and studies on test articles which are not widely used.

11. Several comments closely related to the concerns expressed in paragraph 10 of this preamble requested that further language be added to the regulation exempting certain specific types of studies from coverage.

The Commissioner has reviewed the requests and has chosen not to change the language of the regulation itself to exclude specific study types other than those already mentioned (e.g., studies utilizing human subjects). The regulations apply to any study conducted to provide safety data in support of an application for a research or marketing permit for an FDA-regulated product, and a specific type of study which may be important in the overall safety evaluation of one type of regulated product may not be important in evaluating another. The Commissioner believes it useful to identify in this preamble further examples of studies that are—or are not—within the scope of the GLP regulations.

Examples of studies that are not within the scope of these GLP regulations include:

a. Clinical tests performed solely in conjunction with product efficacy.

b. Chemical assays for quality control.

c. Stability tests on finished dosage forms and products.

d. Tests for conformance to pharmacopeial standards.

e. Pharmacological and effectiveness studies.

f. Studies to develop new methodologies for toxicology experimentation.

g. Exploratory studies on viruses and cell biology.

h. Studies to develop methods of synthesis, analysis, mode of action, and formulation of test articles.

i. Studies relating to stability, identity, strength, quality, and purity of test articles and/or control articles that are covered by good manufacturing practice regulations.

Further examples of types of tests not covered include:

a. Food additives: Tests of functionality and/or appropriateness of the product for its intended use; tests of extractability of polymeric materials that contact food; and all chemical tests used to derive the specifications of the marketed product.

b. Human and animal drugs: Basic research; preliminary exploratory studies; pharmacology experiments; studies done to determine the physical and chemical characteristics of the test article independent of any test system; and clinical investigations.

c. Medical devices: All studies done on products that do not come in contact with or are not implanted in man.

d. Diagnostic products: Essentially all are excluded.

e. Radiation products: Chemical and physical tests.

f. Biological products: All tests conducted for the release of licensed biologicals described in Part 601 (21 CFR Part 601) of this chapter.

These examples do not represent all the exclusions from the regulations, but provide guidance in applying the agency's safety considerations to specific situations. The defined scope of the regulations is necessarily broad to encompass the wide range of types of safety tests, types of testing facilities and regulated products for which proper safety decisions are important.

12. More than 20 comments sought the addition of specific language exempting various classes of FDA-regulated products, such as medical devices, from coverage by the regulations.

The Commissioner has generally elected not to permit exemptions based on broad categories of regulated products because no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another. Proper safety decisions are important for all these products; accordingly, the processes by which such safety data are collected should be subjected to identical standards of quality and integrity.

13. Several comments said that the animal care provisions should apply only to these nonclinical studies using laboratory animals and should not apply to nonclinical studies which involve large animals.

It is clear that the animal care provisions are directed toward the use of laboratory animals, and therefore certain of these provisions may not apply to studies not involving laboratory animals, such as tissue residue and metabolism studies conducted in cattle. Although these studies do fall within the definition of a nonclinical laboratory study, the animals used in such a study are not generally kept in a laboratory setting. Because the husbandry requirements for laboratory animals differ greatly from those for large animals, the agency does not require that large animals be reared and maintained under the same conditions as laboratory animals. The regulations are revised to include terms such as "when applicable" and "as required" in those provisions for which a wide latitude of acceptable husbandry practice exists.

14. Three comments said the regulations should apply to all studies whether submitted in support of or as a challenge to an "application for a research or marketing permit."

The Commissioner agrees, in principle, that all nonclinical studies should be performed in a manner designed to ensure the quality and integrity of the data. FDA is requiring that, at the time a study is submitted, there be included with the study either a statement that the study was conducted in compliance with Part 58 requirements or, if the study was not conducted in compliance with those requirements, a statement that describes in detail all deviations. This requirement means that, at the time a study not conducted in compliance with the requirements is submitted, the agency may evaluate the effects of the noncompliance and take one of the following actions: (1) Determine that the noncompliance did not affect the validity of the study and accept it, or (2) determine that the noncompliance may have affected the validity of the study

and require that the study be validated by the person submitting it, or (3) reject the study completely. The standard of review applied to studies that contain data adverse to a product is no different. That is, a study that failed to comply with these regulations might, nonetheless, contain valid and significant data demonstrating a safety hazard. Thus, FDA is not proposing a double standard, but is, rather, seeking to address those studies that present the most serious regulatory problems.

The preamble to the proposed regulation (41 FR 51215) discussed this issue as follows:

> Valid data and information in an otherwise unacceptable study which are adverse to the product, however, may serve as the basis for regulatory action.
>
> This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard. It reflects current agency policy; even in situations where the scientific quality of an investigational drug study is not in question, FDA may receive data but not use it in support of a decision to approve testing or commercial distribution because of ethical improprieties in the conduct of the study. (See 21 CFR 312.20).

A positive finding of toxicity in the test system in a study not conducted in compliance with the good laboratory practice regulations, may provide a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that scientifically valid results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product. The treatment of studies conducted by a disqualified testing facility is discussed in paragraph 231a. below.

15. Exemptions from coverage by these regulations were requested for various types of facilities. Requests were received that they not apply to academic, medical, clinical, and not-for-profit institutions.

The public health purpose of these regulations applies to all laboratory studies on which FDA relies in evaluating the safety of regulated products, regardless of the nature of the facilities in which the studies are conducted. The Commissioner finds that granting an exemption based on type of facility would frustrate the intent of the good laboratory practice regulations. Many other comments urged that such exemptions not be considered because the standards applied to nonclinical testing should be uniform. Many of the requests for exemption were based on the idea that academic or not-for-profit institutions conduct primarily basic research and ought, therefore, to be specifically excluded. Insofar as academic institutions are concerned, the Commissioner notes that such institutions conduct significant amounts of commercial testing pursuant to contracts. He also notes that significant levels of noncompliance with GLP requirements have been found in such institutions. Moreover, as noted in paragraph 11, basic research on drugs is outside the scope of these regulations. In short, no justification has been presented to warrant granting an exemption to such a facility, and any such exemption from the regulations by the type of facility collecting safety data would not provide equal application of the principles of good laboratory practice. Product safety decisions are equally important whether data are collected by the largest commercial nonclinical laboratory facility or by the smallest nonprofit facility. Therefore, the data collected in all types of facilities should be subjected to the same standards of quality and integrity. The results of the pilot program show that the proposed regulations represent achievable standards.

16. Exemption of or different standards for studies conducted outside the United States were requested.

These regulations are designed to protect the public health of the American people by assuring the scientific integrity and validity of laboratory studies that the agency relies on in evaluating the safety of regulated products. The same assurance is needed, whether the studies relied on are foreign or domestic in origin. The Commissioner notes that FDA clearly may refuse to accept studies from any nonclinical testing facility, foreign or domestic, that does not follow the requirements set forth in these regulations. To exempt from the requirements imposed on studies conducted in domestic testing facilities a nonclinical study conducted in a testing facility outside the United States that is submitted to FDA in support of an application for a research or marketing permit or to impose different standards for such studies, would only have the effect of discriminating against U.S. firms. Although inspection of a foreign facility may not be made without the consent of that facility, FDA will refuse to accept any studies submitted by any facility that does not consent to inspection. These same conditions apply to other FDA regulations, e.g., the current good manufacturing practice regulations (21 CFR Part 210). a program of inspection of foreign facilities for compliance with those regulations has been conducted by FDA for several years. A similar inspection program of foreign laboratory facilities conducting studies within the scope of this regulation will be conducted; several foreign laboratories were inspected during the pilot program, and mechanisms for such inspections are being worked out with representatives of the responsible regulatory authorities in foreign countries.

DEFINITIONS

The Commissioner received hundreds of comments regarding definitions (§ 58.3). General comments are listed immediately below; comments regarding specific definitions follow in numerical order.

17. Several comments asked that commonly used terms such as "batch," "area," "laboratory," "pathologist," "quality data," "data integrity," "supervisor," and "management" be defined or clarified.

The Commissioner finds that, with the exception of "batch," the terms set out above do not require individual definitions. The term "pathologist" is used in its ordinary sense, as are the terms "supervisor" and "management" and the phrases "quality data" and "data integrity." As a general rule, the regulation defines separately only those words which will be used in a sense which differs from that given in currently accepted dictionaries or words whose meaning will be limited by the regulation. A new definition has been added for the term "batch" because it is used in these regulations in a context different from other agency regulations, e.g., the good manufacturing practice regulations. "Batch" in these regulations means a specific quantity of a test or control article that has been characterized according to § 58.105(a).

18. Several comments on § 58.3(b) questioned the applicability of the term "test substance" to medical devices, radiation products, in vitro diagnostic products, and botanical materials.

The Commissioner has reviewed the comments carefully and finds that many of the comments submitted regarding the term "test substance" argued that the term, as defined, did not accurately reflect the scope intended to be covered. Because the term "substance," in common usage, refers to chemical compounds and biological derivatives of more or less defined composition, and because the term is not commonly understood to include devices or electronic products, the Commissioner has changed the term "test substance" to "test article." The term "article" is intended to include all regulated products which may be the subject of an application for a research or marketing permit as defined in § 58.3(e).

The Commissioner has deleted the reference to botanical materials because all botanical materials subject to

FDA jurisdisction are adequately encompassed by the other articles specifically mentioned in the definition.

19. Clarification of the term "control substance" (§ 58.3(c)) was requested. Several comments asked whether the term was to include carrier substances and solvents and vehicles. Other comments sugested this term could be confused with the same term used by the Drug Enforcement Administration.

The term is changed to "control article" to parallel the revised definition for test article. This change avoids any potential conflict with definitions used by other agencies. The term is intended to define those materials given to control groups of test systems for establishing a basis of comparison. The Commissioner recognizes that for certain nonclinical laboratory studies, no control groups are used, and therefore this definition would not apply. For example, testing the safety of implantable pacemakers in animals would require either no control animals or animals that have only been "sham-operated." The definition includes carrier materials when such carrier materials are given to control groups within test system and likewise for administered vehicles and solvents. The term also applies to articles used as positive controls.

20. Many comments on § 58.3(d) addressed the definition of the term "nonclinical laboratory study." A great many, if not the majority, of the comments sought to change the definition by adding language excluding certain specific tests, products, or types of laboratories.

The Commissioner notes that many of these comments overlap with or are identical to comments submitted in response to § 58.1 (Scope). To the extent that the comments and issues are the same, they have been dealt with in the discussion of § 58.1, above. Other comments are dealt with specifically below.

21. Many comments stated that the proposed language which included studies intended to assess the functionality and/or effectiveness of a test article should be deleted. One comment stated that efficacy testing in nonclinical tests is, by definition, preliminary and should be excluded to be consistent with the scope defined in § 58.1. Other comments stated that the language was too broad and too ambiguous and could be interpreted to include many studies which were not safety studies at all.

The Commissioner has considered these comments and agrees that the language related to functionality and/or effectiveness is too broad. He has, therefore, deleted the sentence.

22. Several comments requested that the last sentence of § 58.3(d) be modified by deleting the proposed examples of tests.

The Commissioner finds that the examples included in the proposal tended to confuse rather than clarify. The examples, therefore, have been deleted.

23. Section 58.3(e), which defines the various types of submissions to FDA, was criticized for use of the term "application for research or marketing permit." Several comments said the term was misleading because not all products are regulated through the use of "permits."

The Commissioner believes the term is appropriate for the purpose of these regulations. As stated in the proposal, this definition includes all the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing marketing of a product. The term is intended solely as a shorthand way of referring to the separate categories of data (identified in the proposal) that are now, or in the near future will become, subject to requirements for submission to the agency.

24. One comment stated that proposed § 3e.3(e)(14) should be deleted because the language was overly broad and because it contradicted the intent expressed in the preamble to limit GLP regulations to safety studies.

The Commissioner notes that the preamble to the proposal (41 FR 51209) stated that studies conducted to determine whether a drug product conforms to applicable compendial and license standards were excluded from the regulation. Safety data submitted to obtain the initial licensing of a biological product are covered by these regulations in § 58.3(e)(13). Once a biological is licensed, however, it becomes subject to testing procedures similar to compendial testing procedures. The Commissioner finds that postlicensing testing of biologicals is conducted more for quality control purposes than for establishing the basic safety of the biologic product and has, accordingly, deleted postlicensing testing from the definition of research and marketing permit.

25. Several comments stated that in vitro diagnostic tests (proposed § 3e.3(e)(15)) should not be included because in vitro diagnostic products do not come in contact with patients and do not, therefore, require preliminary animal safety testing.

Because in vitro diagnostic products do not require any nonclinical laboratory tests for agency approval, the Commissioner agrees that in vitro diagnostic products need not be included in the definition "application for a research or marketing permit." Proposed § 3e.3(e)(15) has, therefore, been deleted from the final regulation.

26. Several comments objected to the inclusion of medical devices in § 58.3(e) (16), (17), and (18), stating that medical devices were not "test substances," that medical devices should not be included because the rules for data submission for such devices were as yet undefined, and that inclusion of medical devices would be unduly restrictive. These comments suggested either total or partial exclusion from coverage under the good laboratory practice regulations.

For reasons stated previously, the Commissioner does not agree that medical devices, as a category, should be excluded. Implantable devices may be composed of polymeric materials that contain components capable of leaching from the device into the body of the recipient or may themselves be adversely affected by body constituents. In either case, safety studies would be necessary to demonstrate that components of the device did not cause harm or that the body constituents did not promote breakdown or malfunction of the device.

27. Comments also requested deletion of all terms relating to radiation products in § 58.3(e) (20), (21), and (22), stating that to include such products would restrict experimentation unduly, and arguing that radiation products were not "test substances."

The Commissioner rejects these comments. The quality and integrity of the safety data are no less important for radiation products than they are for other agency-regulated products. He does not agree that including radiation products will unduly restrict experimentation. The remaining argument is covered in the discussion of "test article" above. A new paragraph § 58.3(e)(19) is added to cover data and information regarding an electronic product submitted as part of the procedure for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation performance standard, described in Subpart D of Part 1003 (21 CFR Part 1003).

28. Many comments stated that the term "sponsor" in § 58.3(f) was too broadly defined. For example, two comments stated that the definition, as written, would cover a company which provides a grant to a university, a fact which, if true, would inhibit giving grants. One comment said that the definition is so broad that it could be interpreted to apply to stockholders.

The Commissioner advises that a person providing a grant may be a sponsor. In the area of nonclinical laboratory studies, most grantors ulti-

mately submit the data to the agency. The Commissioner does not agree that because the definition of "sponsor" includes grantors it will inhibit the giving of grants. No data were submitted to support this argument. The Commissioner further advises that the definition does not include stockholders.

29. Other comments on § 58.3(f) asked whether the regulation allowed for multiple sponsors and whether government agencies could be sponsors.

"Person," as defined in § 58.3(h), includes government agencies, partnerships, and other establishments such as associations. Therefore, a government agency can clearly be a sponsor. In addition, the Commissioner advises that the definition does not preclude joint sponsorship of a study.

30. Several comments asked that the definition of "testing facility" in § 58.3(g) be revised to indicate clearly that a facility conducting a study subject to the regulations should be subject only to the extent that the facility is involved with and responsible for the study.

The Commissioner concludes that no revision to the definition is necessary. The definition clearly does indicate that a facility is covered by the regulations only to the extent that the facility is conducting or has conducted nonclinical laboratory studies.

31. Numerous comments addressed the definition of "test system" in § 58.3(i). Eighteen comments stated that the definition, as written, could be interpreted to require testing of beakers and test tubes. Two comments pointed out that the "test system" is not the container being tested for extractables, but rather it is the animal, microorganism, or cellular components used to test the extractables for safety.

The Commissioner has carefully reviewed the proposed definition in light of the comments and has made a number of changes. The terms "cellular and subcellular" have been replaced for clarity with "subparts thereof" which refers to animals, plants, and microorganisms. The revised definition now reads: "'Test system' means any animal, plant, microorganism, or subparts thereof, to which the test or control article is administered or added for study. 'Test system' also includes appropriate groups or components of the system not treated with the test or control articles." The revisions should make the definition clearly consistent with § 58.3(d) ("nonclinical laboratory study"), which states that studies to determine physical or chemical characteristics of a test article or to determine potential utility are not included. Therefore, testing of beakers and test tubes, which fall into the category of physical and chemical tests, is excluded.

32. Section 58.3(j), which defines "specimen," drew several comments. These included requests for precise definition of the terms "material" and "tissue" and requests for a clearer definition of the term "specimen."

The Commissioner is modifying the term "specimen" to include any material derived from a test system for examination or analysis. Under these circumstances, blood, serum, plasma, urine, tissues, and tissue fractions are all included if they are intended for further examination or analysis. The definition includes all materials that yield data related to the safety decision on a regulated product.

33. Many comments were received on the definition of "raw data" in § 58.3(k). Included were requests to clarify the term "certified" and to state whether carbons, photocopies, and written reports of dictated material could be classified as "raw data". Other issues concerned whether financial information and first drafts of reports were "raw data."

The Commissioner concludes that the proposed definition should be clarified. The word "exact" is substituted for the word "certified." "Certified" connotes a legal document that requires notarization; "exact" has no such connotation and more precisely reflects the Commissioner's intention. The definition is further clarified by inserting, after the first sentence, a new sentence which reads: "In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data." This clarification will permit data collection by tape recorders without requiring the retention of the original tapes. Carbons and photocopies satisfy the regulations, provided they are exact and legible copies of the original information. Neither financial information nor first drafts of reports are raw data within the meaning of the term.

34. Several comments said only recorded data contributing substantially to the study should be retained and, similarly, only computer printouts contributing substantially should be retained. Several comments requested clarification of the method for storing machine-generated data and definition of "on line data recording system."

Because the parenthetical example ("derived from on-line data recording systems") served more to confuse than to clarify, it has been deleted. However, an "on line data recording system" pertains to an instrument that can feed data directly into a computer that analyzes and stores the information. The product of this activity usually consists of a memory unit plus a computer program for extracting the information from the unit. Hard-copy computer printouts are unnecessary, provided the computer memory and program are accompanied by a procedure that precludes tampering with the stored information.

The Commissioner cannot agree that only those portions of the data that contribute substantially to the study need to be retained. Such an approach would require a judgment to be made which, if in error, could lead to improper or incorrect study reconstruction. The purpose of retaining the raw data is to permit the quality assurance unit and agency investigators to reconstruct each phase of a nonclinical laboratory study. Discarding essential records would frustrate this purpose. Raw data may be stored in separate areas provided the archival indexes give the data location.

35. Many comments addressed "quality assurance unit" in § 58.3(l).

The Commissioner has reviewed these comments and concludes that they are more concerned with the concept of the quality assurance unit than with the definition. The comments are therefore dealt with in detail in that section of the preamble concerned with § 58.35 of the regulations. (See paragraphs 75 through 92 below.)

36. Several comments addressed "study director" in § 58.3(m). These comments requested clarification, permission to have more than one study director per study, and that the term "implementation" be changed to "conduct."

The Commissioner has revised the definition to read: "'Study Director' means the individual responsible for the overall conduct of a nonclinical laboratory study." The revision is intended to emphasize that the study director is responsible for the entire study, as well as being responsible for the interpretation, analysis documentation, and reporting of results.

The Commissioner concludes that the other comments received on the definition of "study director" addressed the concept rather than the definition, and these comments are dealt with under the discussion of § 58.33 (see paragraphs 59 through 74, below).

APPLICABILITY TO STUDIES PERFORMED UNDER GRANTS AND CONTRACTS

37. Two comments requested revision of § 58.10 to specify clearly that the sponsor is ultimately responsible for data validity, even if the data are obtained by a sponsor from a grantee or contractor.

The Commissioner concludes that no revision of § 58.10 is necessary. All persons involved in a nonclinical laboratory study are responsible for part or all of the study, depending upon the extent of their participation. Athough a sponsor who submits studies to FDA bears the responsibility for the work performed by a subcontractor or grantee, that fact in no way relieves a grantee or subcontractor from individual responsibility for the portion of the study performed for the sponsor. Indeed, the purpose of the requirement that the sponsor notify a grantee or subcontractor that the work being performed is a part of a nonclinical laboratory study which must be conducted in compliance with the good laboratory practice regulations is to assure that all parties submitting data are aware of their responsibilities under the regulation.

38. Several comments requested exemption for certain specialized services which are not commonly available, e.g., ototoxicity studies with diuretics. The comments stated that these specialized services would probably not be available to them if the stringent requirements of the regulations had to be met by the service organization.

The Commissioner concludes that certain specialized services cannot be exempted from these regulations. The specialized services may contribute in large measure to the agency decision to approve a research or marketing permit. If the studies are intended to provide safety data in support of an application for a research or marketing permit, their conduct falls within the scope of these regulations.

INSPECTION OF A TESTING FACILITY

39. Comments on the inspection provisions (§ 58.15) expressed concern regarding the competence and scientific qualifications of FDA investigators.

The agency has endeavored, through a specialized training program, to assure that FDA investigators are competent to perform good laboratory practice inspections. The EILP program is new, and training and evaluation will continue to improve it. The results of the pilot inspection program and the manner in which it was coducted should provide added assurance to testing facility management regarding the competence of FDA investigators. The quality of the program is not, however, dependent on the competence or training of any single individual. Inspection of findings are always subject to supervisory review within the agency, and no official action may be taken without concurrence of a number of qualified persons.

40. Several comments stated that agency inspection should be limited to those facilities under current FDA legal authority.

The scope of the regulations and the definition of a "nonclinical laboratory study" define those studies covered by the regulations. The agency intends to inspect all facilities which are conducting such studies. Many of these facilities are subject to inspection under express statutory authority vested in FDA. As noted in the preamble to the proposal (41 FR 51220):

> Inspections of many, perhaps most, testing facilities will not be conditioned upon consent. Under section 704(a) of the act, FDA may inspect establishments including consulting laboratories, in which certain drugs and devices are processed or held, and may examine research data that would be subject to reporting and inspection pursuant to section 505 (i) or (j) or 507 (d) or (g) of the act. In addition, any establishment registered under section 510(h) of the Act is subject to inspection under section 704 of the act. Thus, most manufacturing firms that conduct in-house non-clinical laboratory studies on drugs and devices, and those contract laboratories working for such firms, would be subject to FDA inspection whether or not they consented.

Facilities that are not subject to statutory inspection provisions will be asked to consent to FDA inspection. The absence of any statutory authorization does not bar FDA from asking permission to conduct an inspection, and the agency should not bar itself from seeking permission. Thus, the proposal in the comment is not accepted.

41. Several comments requested that FDA make its enforcement strategy known as promised in the preamble to the proposal.

The enforcement strategy was discussed in the preamble to the proposal (41 FR 51216) and is amplified in the compliance program which implements this regulation. The compliance program is publicly available and may be obtained by sending a written request to the agency official whose name and address appear at the beginning of this preamble as the contact for further information.

42. Two comments on § 58.15 as proposed requested that the requirement that the testing facility permit inspection by the sponsor be deleted. The comments argued that the rights and obligations of a sponsor and its laboratory are a matter of contract between them alone, and not a proper subject for government regulation.

The Commissioner has considered this issue, is persuaded that the comments are correct, and has deleted the phrase "the sponsor of a nonclinical laboratory study." At the same time, however, the Commissioner reemphasizes that, because a sponsor is responsible for the data he or she submits to the agency, the sponsor may well wish to assure that the right to inspect a testing facility is included in any contract.

43. Other comments suggested that the sponsor should accompany the FDA investigator during an inspection of a contract testing facility and that FDA access to data should require the sponsor's consent.

The Commissioner disagrees with these comments. An agency investigator may be inspecting the results of studies from several sponsors during an inspection. The logistics required to notify and arrange for several sponsors to accompany an investigator, or to obtain sponsor consent to information release, would be unworkable. FDA's practice of unannounced inspections has proved to be an effective and efficient use of scarce resources. Because of resource limitations, FDA cannot inspect each facility as often as it would like to, and the Commissioner finds that the possibility of unannounced FDA inspections at any time motivates compliance.

44. Many comments were concerned that trade secret information obtained during the inspection would be released by FDA.

The Commissioner notes that trade secrets obtained as a result of an inspection are fully protected under the provisions of section 301(j) of the act (21 U.S.C. 331(j)), as well as 18 U.S.C. 1905 and the Freedom of Information Act (5 U.S.C. 552(b)(4)) and the FDA's implementing regulations (21 CFR 20.61). Interested parties may refer to the agency's public information regulations (21 CFR Part 20), which govern agency release of documents.

45. One comment requested that the results of government laboratory inspections be made public.

The Commissioner notes that no distinctions will be made between government or nongovernment laboratories. The results of an inspection of testing facilities will be available after all required followup regulatory action has been completed.

46. The phrase "and specimens" has been added to § 58.15(a). The Commissioner finds that examination of specimens may be required to enable the agency, where necessary, to reconstruct a study from the study records.

47. Many comments stated that the inspection of records should not extend to certain records compiled by the quality assurance unit.

The Commissioner agrees and has exempted from routine inspection those records of the quality assurance unit which state findings, note problems, make recommendations, or evaluate actions taken following recommendations. These exemptions from inspection are discussed in greater detail under the discussion of § 58.35.

48. A new paragraph (b) has been added to § 58.15. This paragraph is similar to proposed § 58.200 and reiterates that a determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not relieve an applicant from any obligation under any applicable statute or regulation (e.g., 21 CFR Parts 312, 314, 514, etc.) to submit the results to FDA. If a testing facility refuses inspection of a study, FDA will refuse to consider the study in support of an application for a research or marketing permit. This refusal, however, does not relieve the sponsor from any other applicable regulatory requirement that the study be submitted.

ORGANIZATION AND PERSONNEL

PERSONNEL

49. A number of comments addressed the definition of training, education, and experience in § 58.29. Several comments considered such references too vague; several others suggested that appropriate qualifications be established by professional peer groups.

It would be inappropriate, if not impossible, for FDA to specify exactly what scientific disciplines, education, training, or expertise best suit a specific nonclinical laboratory study. These factors, which vary from study to study, are left to the discretion of responsible management and study directors. They are responsible for personnel selection and for the quality and integrity of the data these personnel will collect, analyze, document, and report. The Commissioner urges, however, that management and study directors carefully consider personnel qualifications as they relate to a particular study. The agency has uncovered instances, discussed in the preamble of the proposal (41 FR 51207), in which the conduct of a study by inadequately trained personnel resulted in invalid data. Although the Commissioner recognizes the value of certification by professional peer groups, he does not agree that the concept is appropriate for regulatory purposes.

50. Several comments said the study director should be given responsibility for assurance of qualifications of personnel.

The Commissioner agrees that, generally, the study director will be responsible for ensuring that personnel selected to conduct a nonclinical laboratory study meet necessary educational, training, and experience requirements. The Commissioner notes, however, that management also has selection and hiring responsibilities and privileges.

51. One comment stated that the requirement of § 58.29 that each individual engaged in the conduct of a study have sufficient training or experience to enable the individual to perform the assigned function should be limited to those personnel engaged in supervision and collection and analysis of data.

The Commissioner disagrees. These factors are important and should be considered for personnel other than supervisors or those engaged in collection and analysis of data. The approach suggested by the comment would ignore the fact that specific expertise is required, for example, by animal caretakers, physical science technicians, and by persons using pesticides near animal-holding areas. While the degree of education, training, and experience necessary for these positions will be quite different from the qualifications necessary for supervisors or scientific staff, the need for sufficient training or experience is no less important.

52. One comment pointed out the appropriateness of changing the term "person" to "individual" in § 58.29(a).

Because the term "person" as defined in § 58.3(h) includes partnerships, corporations, etc., the Commissioner agrees that "individual" is the proper term and has so amended § 58.29(a).

53. Seventeen comments questioned the use of, or objected to reference to, the term "curriculum vitae" for nontechnical personnel such as animal caretakers, as required in proposed § 58.29(b).

Another comment asserted that the requirement infringed on management's prerogatives without specifying how any such infringement occurred. One comment stated that the requirement that such records be retained after termination of employment was unnecessarily cumbersome.

The Commissioner does not agree that the requirement infringes on management's prerogatives. However, the Commissioner agrees with the remaining comments and has revised the section. "Curriculum vitae" has been changed to "summaries of training and experience plus job descriptions." Reference to the maintenance of records of terminated employees is deleted from this section because the requirement is redundant to the record retention requirements set forth in § 58.195(e).

54. Ten comments said the wording of § 58.29(c), relating to "sufficient numbers of personnel" and to "timely" conduct of the study, was vague.

The Commissioner purposely left the paragraph broad in context and coverage because differences in types of studies preclude any specific approach to defining numbers of personnel. The precise number of personnel reuired for a specific study, as well as for all ongoing studies, is a management decision. FDA experience, however, indicates that a shortage of qualified personnel can lead to inadequate or incomplete monitoring of a study and to delayed preparation and analysis of results, and the numbers of personnel conducting a study should be sufficient to avoid these problems.

55. Ten comments requested deletion of § 58.29(d) or clarification of the language regarding employee health habits, stating that the section was too vague and that an employer was responsible for health habits only at work. One comment submitted alternate language.

The Commissioner adopts with modifications the alternate language. The paragraph now requires only that personnel take necessary personal sanitation and health precautions to avoid contamination of test and control articles and test systems.

56. Several comments asked that the term "laboratory" in § 58.29(e), as applied to protective clothing, be deleted because it is too restrictive. Other comments suggested that the requirement that clothing be changed as often as necessary to prevent contamination be eased by changing "prevent" to "help prevent." Four related comments requested modification to reflect only "contamination affecting validity of studies."

The Commissioner agrees to the elimination of "laboratory" as applied to clothing. The provision of specialized clothing is, however, an estalished and well-known procedure for preventing contamination in a variety of situations. The Commissioner disagrees with any suggested modification of this section which weakens the intent of the regulation. The objective is to prevent contamination of the test system.

57. A number of comments addressed several aspects of § 58.29(f) regarding personal illnesses, personal health records, types of illnesses, and records of illnesses. Comments said disclosure of medical records was an invasion of privacy and of little relevance to the proper conduct of a nonclinical laboratory study.

The Commissioner agrees that documentation of personal illnesses may constitute an unwarranted invasion of privacy, and this requirement is deleted. The Commissioner disagrees with the requests for deletion of the entire paragraph, noting the relationship between personnel health and possible contamination of test systems. Revised § 58.29(f) requires individuals with illnesses that may adversely affect the quality and integrity of nonclinical laboratory studies to be excluded from direct contact with test and control articles and test systems.

The Commissioner has deleted from § 58.35(a) the sentence in question. The QAU of the testing facility is solely responsible for fulfilling the quality assurance functions for studies conducted within that facility. In those cases where portions of a study, e.g., feed analysis, are performed by a contract facility which, because it is not itself a nonclincial facility, does not have a QAU, the person letting the contract, and not the contract facility, is responsible for the performance of the quality assurance functions.

The Commissioner believes that the mechanism by which a sponsor is assured of the quality of nonclinical studies performed for it under contract is a matter that can be left to the contracting parties and need not be addressed in these regulations.

80. Three comments suggested that testing facilities be licensed or certified in lieu of having an ongoing quality assurance unit.

The Commissioner considered such an approach and rejected it before publishing the proposed regulations. (See 41 FR 51208-51209.) No persuasive arguments for changing this decision were presented in the comments. The diversity in the size and nature of nonclinical testing facilities subject to the provisions of these regulations makes licensing or certification procedures impractical. The regulation is intended to assure the quality and validity of the data obtained by each nonclinical laboratory study, and the QAU provides a mechanism to monitor each ongoing study. Licensing a testing facility could not achieve the same result.

81. Many comments objected to the provisions of § 58.35(b)(1) which require that the quality assurance unit maintain a master schedule sheet of all nonclinical laboratory studies. Some comments believed the requirement was excessive, while others questioned the proposed format and contents of the list. One comment pointed out that not every study includes all items listed.

The Commissioner is convinced that maintenance of a master schedule sheet is essential to the proper function of the Quality Assurance Unit. Only through such a mechanism can management be assured that the facilities are adequate and that there are sufficient numbers of qualified personnel available to accomplish the protocols of all nonclinical studies being conducted at a facility at any given time.

Upon careful review of the items required to be listed, the Commissioner agrees that the requirement that animal species be identified may be deleted because the requirement that "test system" be listed adequately covers this point. He has, in addition, deleted the examples of study types because he agrees that including the information is not necessary to achieve objectives of this section. The Commissioner has further reworded this section to eliminate reference to whether the final report has been approved for submission to the sponsor because the language was strictly applicable only to studies done under contract. The revised language simply requires that the status of the final report be listed.

82. Nine comments objected that § 58.35(b)(2) required too much duplicative paper.

The Commissioner has concluded that the QAU must maintain copies of study protocols to assure that they are followed and amended in accordance with the further provisions of these regulations. The Commissioner agrees that the requirement that the QAU maintain copies of all standard operating procedures would substantially increase the volume of records needed to be retained by this unit. Because there should be many copies of standard operating procedures present throughout the facility which should be freely available to QAU members, the Commissioner has deleted the requirement that these be maintained by the QAU.

83. Fifteen comments suggested that § 58.35(b)(3) be deleted on the basis that FDA should not dictate how the QAU achieves its objectives. One comment suggested that "inspect" be changed to "audit."

The Commissioner remains convinced of the need for a formal mechanism through which the QAU maintains oversight of the conduct of a study. Such a mechanism must be based on direct observation in order that the independence of the QAU be preserved. The Commissioner has retained the word "inspect" in preference to "audit." "Inspect" more accurately conveys the intent that the QAU actually examine and observe the facilities and operations for a given study while the study is in progress, whereas "audit" could be interpreted to mean simply a detailed review of the records of a study. Because the QAU function is to observe and report the state of compliance with the regulations and to determine whether the protocol is being followed rather than to verify the results of a study, "inspect" more properly conveys the agency's intent.

84. Fourteen comments addressed the need to inspect "each phase of a study * * * periodically," seeking clarification or different language. Nine of these comments called for the use of random sampling procedures in choosing studies or phases of studies to inspect in order to decrease the workload and resource requirements of the QAU.

The Commissioner does not agree that random sampling would be an adequate method of evaluation in the nonclinical laboratory setting. In situations which involve the repetition of similar or identical procedures, random sampling can provide an adequate means of quality control. Here, however, the differences among study operations and among the personnel conducting them invalidate any assumption that the conduct of one phase of one study is representative of the conduct of that phase of another or of other phases of a single study. The term "each phase" is intended to emphasize the need for repeated surveillance at different times during the conduct of a study so that each critical operation is observed at least once in the course of the study. The term "periodically" is retained to indicate the need for more than one inspection of certain repetitive continuing operations that are part of the conduct of longer term studies such as animal observations and diet preparation.

85. Many comments objected to the proposed requirement that any problems found by the QAU be brought to the attention of management and appropriate responsible scientists. Some felt that this would require that excessive resources be spent on minor problems. Others felt that notification of appropriate supervisory personnel rather than management was sufficient.

The Commissioner agrees that only those problems likely to affect the outcome of the study need to be brought to the immediate attention of personnel who are in a position to resolve those problems, and the language of § 58.35(b)(3) has been changed accordingly. The term "management" in its ordinary usage means appropriate supervisory personnel and has not, therefore, been changed.

86. More than 40 responses to proposed § 3e.33(b)(4) objected to the specific time frames required for evaluation. Several comments suggested that the paragraph be deleted. Others objected to the specific requirements, and still others stated that appropriate times for evaluatuations should be selected by management.

The Commissioner advises that periodic inspection is necessary and that the time periods specified are the minimum required to assure that a study is being conducted in compliance with the regulation. Should deviations be found during the periodic inspections, there may still be time to take corrective action. The Commissioner has, however, determined that inspection of studies lasting less than 6 months need only be conducted at intervals adequate to assure the integri-

ty of the study and that specific time intervals for such studies need not be set out in this regulation. The requirement that studies lasting more than 6 months be inspected every 3 months remains unchanged. The section has been added to § 58.35(b)(3).

87. Several comments requested that the phrase "complete evaluation" in proposed § 3e.33(b)(4) be clarified.

The Commissioner has changed the term "complete evaluation" to "inspect." The function of the QAU is to inspect studies at specified intervals to maintain records required by this regulation, and to report to management and the study director deviations from the protocol and from acceptable laboratory practice. Evaluation of any reported deviations is left to the study director and to management.

88. Fifteen comments sought deletion of § 58.35(b)(4), which requires the periodic submission of status reports to management and the study director. Three comments questioned the need to note problems and corrective action taken.

The Commissioner has retained this provision as proposed. Only through the submission of such status reports can management be assured of the continuing conformity of study conduct to the provisions of these regulations. Because § 58.35(b)(3) has been revised to require that only significant problems be reported immediately to management, the periodic status report becomes even more important as a means of informing management of minor problems and normal study progress. The status reports are needed to document problems and corrective actions taken so that management can be certain that quality is being maintained and that management intervention is not required. The timing of such reports may be determined by management.

89. Six comments objected that the term "prior" preceding "authorization" in § 58.35(b)(5) was too restrictive. The comments pointed out that unforeseen circumstances may prevent prior authorization for deviations from standard procedure and that the QAU should be concerned with the documentation of the deviation, not with whether prior authorization existed. Two comments stated that the QAU cannot assure that deviations do not occur but can determine, by inspection, whether deviations were documented.

The Commissioner is persuaded that prior authorization cannot always be obtained. For example, a fire in the facility would necessitate immediate action. The Commissioner agrees that documentation of the deviation rather than prior authorization is the important point and has deleted "prior" and added "documentation." In addition, "assure" has been changed to "determine" to respond to the comments and to reflect more accurately the Commissioner's intent. Section 58.35(b)(5) now reads: "Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation."

90. Several comments objected to the wording of § 58.35(b)(6), which states that the QAU shall review the final study report. The comments stated that such review requires a scientific judgment and is not an appropriate function for the QAU to perform. One comment suggested that the requirement should be modified to allow for random sampling rather than a complete review of all studies.

The Commissioner agrees that the QAU should not attempt to evaluate the scientific merits of the final report. Therefore, he has modified the paragraph. The QAU must however ensure that the final report was derived from data obtained in accordance with the protocol. Data in the final report significantly contributing to the quality and integrity of a nonclinical laboratory study shall be reviewed. A random sampling approach is not acceptable.

90a. The Commissioner has added to § 58.35 new paragraph (b)(7) which requires that the QAU prepare and sign a statement to be included with the final report which specifies that dates inspections of the study were made and findings reported to management and the study director. This requirement clarifies the fact that QAU review should extend through the completion of the final report and provides a mechanism for documenting that the review has been completed. A conforming section has been added to the final report requirements of § 58.185 as new paragraph (a)(14).

91. Many comments argued that requiring all portions of a quality assurance inspection to be available for FDA inspection might serve to negate their value as an effective management tool for ensuring the quality of the studies during the time in which the studies are being conducted.

The Commissioner shares the concerns of the comments that general FDA access to QAU inspection reports would tend to weaken the inspection system. He believes that FDA's review of quality assurance programs is important, and he recognizes the need to maintain a degree of confidentiality if QAU inspections are to be complete and candid. Therefore, the Commissioner has decided that, as a matter of administrative policy, FDA will not request inspections and copying of either records of findings and problems or records of corrective actions recommended and taken; and §§ 58.15 and 58.35(c) have been revised to separate those records subject to regular inspection by FDA from those records not subject to such inspection. Exempt from routine FDA inspection are records of findings and problems as well as records of corrective actions recommended and taken. All other records are available. Although the Commissioner is deleting the requirement in new § 58.35(d) that testing facility management shall, upon request by an authorized employee, certify in writing that the inspections are being performed and that recommended action is being or has been taken. Upon receiving such a request, management is required to submit the certification of compliance. A person who submits a false certification is liable to prosecution under 18 U.S.C. 1001.

The one exception to FDA's policy of not seeking access to records of findings and problems or of corrective actions recommended and taken is that FDA may seek production of these reports in litigation under applicable procedural rules, as for otherwise confidential documents.

92. Many comments objected that requiring internal quality assurance audits to be available to the agency might violate the constitutional privilege against compelled self-incrimination.

The Commissioner disagrees with the comments. It is settled that the privilege against compelled self-incrimination is an individual privilege relating to personal matters; the privilege is not available to a collective entity, such as a business enterprise, or to an individual acting in a representative capacity on behalf of a collective entity. *California Bankers Ass'n* v. *Schultz*, 416 U.S. 21, 55 (1974); *Bellis* v. *United States*, 417 U.S. 85 (1974); *United States* v. *Kordel*, 397 U.S. 1, 8 (1970); *Curcio* v. *United States*, 354 U.S. 118, 122 (1957); *United States* v. *White*, 322 U.S. 694, 699 (1944); *Wilson* v. *United States*, 221 U.S. 361, 382-384 (1911); *Hale* v. *Henkel*, 201 U.S. 43, 74-75 (1906). Even for individuals, the privilege against compelled self-incrimination is inapplicable where a reporting requirement is applied to an "essentially noncriminal and regulatory area of inquiry," where self-reporting is the only feasible means of securing the required information, and where the requirement is not applied to a "highly selective group inherently suspect of criminal activities" in an "area permeated with criminal statutes." *California* v. *Byers*, 402 U.S. 424, 430 (1971); *Marchetti* v. *United States*, 390 U.S. 39 (1968); *Albertson* v. *SACB*, 382 U.S. 70, 79 (1965); *Shapiro* v. *United States*, 335 U.S. 1 (1948).

ACCESS TO PROFESSIONAL ASSISTANCE

93. Comments on proposed § 3e.35 suggested rephrasing the statement to specify that professional assistance be authorized by the study director, that it be either in person or by telephone, that it be available within a reasonable period, and that reference to availability of a veterinary clinical pathologist be included. Other comments suggested that the concept was duplicative of the function of the study director and should be deleted.

The Commissioner proposed this requirement to assure that a scientist or other professional would be available to respond to requests for assistance or consultation from less experienced personnel. However, because management is responsible for assuring that personnel are available and that personnel clearly understand the functions they are to perform, and because the study director has overall responsibility for the technical conduct of the study, access to professional assistance is a matter best left to management's discretion. Therefore, the section is deleted from the final regulations.

FACILITIES

GENERAL

94. Many comments requested definition or clarification of the terms denoting separation (i.e., separate area, defined area, separate space, and specialized area), which are used in §§ 58.41, 58.43, 58.47, 58.49, and 58.90.

The Commissioner's intent in proposing that there be defined (and, where required, separate or specialized) areas in a testing facility was to assure the adequacy of the facility for conducting nonclinical laboratory studies. This intent is more clearly stated in the revised second sentence of § 58.41, which now reads: "It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study." The important point is that the facility be designed so that the quality and integrity of the study data is assured. The manner in which the separation is accomplished may be determined by testing facility management.

Adequate separation may be, in various situations, a function of such factors as intended use of the specific part of the facility, space, time, and controlled air. The broad variety of test systems, test and control articles, and the size and complexity of testing facilities preclude the establishment of specific criteria for each situation. For these reasons the Commissioner declines to include in the regulation either a definition or specific examples of methods for achieving adequate separation.

95. One comment suggested that a number of additional animal care and facility requirements be added to the regulations. The suggestions included, e.g., ambience to assure nonstressful conditions; ventilation and room access arranged to prevent cross contamination; and surveillance of animal health before and during a test or experiment.

The Commissioner concludes that no additional requirements need to be added because the regulation, as it stands, adequately covers the additions proposed by the comments. For example, ventilation and room access arranged to prevent cross contamination are addressed by the degree of separation requirement in § 58.41.

ANIMAL CARE FACILITIES

96. Many comments suggested that accreditation of animal care facilities by a recognized organization should provide adequate evidence that a testing facility is in compliance with § 58.43(a). One comment suggested accreditation by recognized organizations for analytical laboratories.

Although the Commissioner is aware of the value of accreditation programs, he cannot delegate FDA's responsibility for determining compliance with these regulations to an organization over which FDA has no authority. Few, if any, accreditation programs cover the same areas covered by this regulation. Furthermore, the Commissioner is unaware of any facility accreditation program which is mandatory. The agency's obligation to inspect a testing facility for overall compliance would not be altered by the fact that a facility was otherwise accredited.

97. Numerous comments objected to the requirements concerning separation of species, isolation of projects, and quarantine of animals as impractical and not necessary in all instances, e.g., separation of species in large animal studies and quarantine of all newly acquired animals. Some of the comments stated that the requirements of this section allow no latitude for judgment concerning their applicability.

The Commissioner reiterates that all requirements may not be applicable or necessary in all nonclinical laboratory studies and that the degree to which each requirement should apply in each case can be determined by informed judgment. Because of the variability of nonclinical laboratory studies, a degree of flexibility in applying the requirements of § 58.43(a) is necessary, and the language of § 58.43(a) is amended to read: "A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals." As noted in the general discussion at the beginning of this preamble, all references to other standards ("The Animal Welfare Act") have been deleted.

98. Several comments suggested that § 58.43(b) be amended to include isolaton of test systems with infectious diseases as well as isolating studies conducted with infectious or otherwise harmful test articles.

The Commissioner agrees that test systems with infectious diseases should be isolated. Proposed § 3e.49(b) provided for specialized areas for handling volatile agents and hazardous aerosols. Section 3e.49(b) also provided for special procedures for handling other biohazardous materials. Proposed § 3e.49(c) provided for special facilities or areas for handling radioactive materials.

To clarify all these requirements, the Commissioner has amended § 58.43(b) to read: "A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents." The provisions in proposed § 3e.49(b) and (c) regarding specialized areas for handling volatile agents, hazardous materials and radioactive materials are deleted from § 58.49.

99. One comment on § 58.43(c) suggested that, in addition to the area designated for the care and treatment of diseased animals, a separate area should be provided for animals with contagious diseases.

The Commissioner agrees, and the paragraph is amended to allow for an area for treatment of animals with contagious diseases, and it is to be separate from the area designated for the care and treatment of diseased animals.

100. Several comments questioned the requirement for separate areas for diseased animals, indicating that often such animals are sacrificed rather than treated.

The Commissioner does not agree that a separate area is not always needed for diseased animals. Although diseased animals may be sacrificed, this is not always the case, and it may not always be possible immediately to sacrifice diseased animals. Thus, a separate area should be available for such animals until sacrifice can be accomplished.

101. One comment requested that § 58.43(e), which deals with facility design, construction, and location to minimize disturbances that interfere with the study, should also define the

Federal Register

FRIDAY, DECEMBER 22, 1978
PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

[4110-03-M]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 76N-0400]

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The agency is issuing final regulations regarding good laboratory practice in the conduct of nonclinical laboratory studies. The action is based on investigatory findings by the agency that some studies submitted in support of the safety of regulated products have not been conducted in accord with acceptable practice, and that accordingly data from such studies have not always been of a quality and integrity to assure product safety in accord with the Federal Food, Drug, and Cosmetic Act and other applicable laws. Conformity with these rules is intended to assure the high quality of nonclinical laboratory testing required to evaluate the safety of regulated products.

EFFECTIVE DATE: June 20, 1979.

FOR FURTHER INFORMATION CONTACT:

Paul D. Lepore, Bureau of Veterinary Medicine (HFV-102), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, (301-443-4313).

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) is establishing regulations in a new Part 58 (proposed as Part 3e) in Title 21 (21 CFR Part 58) regarding good laboratory practice. These constitute the first of a series of regulations concerning investigational requirements which are being developed as a result of the FDA Bioresearch Monitoring Program. Proposed regulations, providing interested persons 120 days to submit comments, were published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206). In addition, public hearings were held on February 15 and 16, 1977 for the presentation of oral testimony on the proposal. Twenty-two oral presentations were given (transcripts are on file with the Hearing Clerk, Food and Drug Administration), and 174 written comments were received. The comments have been categorized and include the following: manufacturers of regulated products (64), associations (40), medical centers (20), private testing or consulting laboratories (18), educational institutions (15), government agencies (8), individuals (8), and an airport director (1).

In the proposal, regulations were designated as a new Part 3e. This final rule incorporates them into a new Part 58 (21 CFR Part 58). The following redesignation table correlates the new sections with those proposed, and, in most instances, reference to the new sections will be used hereinafter.

New Section	*Old Section*
Subpart A	
58.1	3e.1
58.3	3e.3
58.10	3e.10
58.15	3e.15
Subpart B	
58.29	3e.29
58.31	.....
58.33	3e.31
58.35	3e.33
Subpart C	
58.41	3e.41
58.43	3e.43
58.45	3e.45
58.47	3e.47
58.49	3e.49
58.51	3e.51
58.53	3e.53
Subpart D	
58.61	3e.61
58.63	3e.63
Subpart E	
58.81	3e.81
58.83	3e.83
58.90	3e.90
Subpart F	
58.105	3e.105
58.107	3e.107
58.113	3e.113
Deleted	3e.115
Subpart G	
58.120	3e.120
58.130	3e.130
Subpart J	
58.185	3e.185
58.190	3e.190
58.195	3e.195
Subpart K	
58.200	3e.200
58.202	3e.202
58.204	3e.204
58.206	3e.206
58.210	3e.210
58.213	3e.213
58.215	3e.215
58.217	3e.217
58.219	3e.219

As a part of the overall bioresearch monitoring program that was described in the proposal, a pilot inspection program was carried out to assess the current status of laboratory practice of nonclinical testing facilities to aid in evaluating the relevance of the proposed regulations, and to identify any unanticipated difficulties in implementing an agency-wide monitoring and compliance program for the testing facilities.

The pilot inspection program began in December of 1976 and covered a representative sample of testing facilities. The results of these inspections have been evaluated, and the results of the analysis have been made available to the public as OPE Study 42, "Results of the Nonclinical Toxicology Laboratory Good Laboratory Practices Pilot Compliance Program." Notice of availability of this report was published in the FEDERAL REGISTER of October 28, 1977 (42 FR 56799).

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GENERAL ISSUES

1. Many of the written responses to the proposal were in two parts: a discussion of broad issues and a critique of the regulations by section and paragraph. Over a thousand individual items have been considered.

2. Thirty-two comments requested republication of the proposed regulations as guidelines.

The Commissioner of Food and Drugs advises that publishing guidelines rather than regulations was considered and rejected before publication of the proposal. The question was considered again in preparation of this order, and again rejected. The seriousness of problems encountered in testing facilities demands the use of an approach that will achieve compliance directly and promptly. Only by specifying the requirements for compliance in detailed, enforceable regulations can the Commissioner be assured of the quality and integrity of the data submitted to the agency in support of an application for a research or marketing permit.

3. Some comments objected to the incorporation by reference of other laws, recommendations, and guidelines as being either redundant or without the authority conferred by rulemaking procedures as required by the Administrative Procedure Act. It was also asserted that such incorporation could lead to confusion.

The Commissioner agrees that these regulations should not duplicate regulations and requirements subject to the purview of other agencies. Therefore, reference to animal care provisions of the Animal Welfare Act of 1970 (Pub. L. 91-570) and recommendations contained in Department of Health, Education, and Welfare (HEW) Publication No. (NIH) 74-23 have been deleted from §§ 58.43(a) and 58.90(a) (21 CFR 58.43(a) and 58.90(a)). Also, all provisions that referred to regulations of the Occupational Safety and Health Administration or were concerned with the health and safety of employees have been revised or deleted, i.e., 21 CFR 58.33(a) (by deletion of proposed 21 CFR 3e.31(a)(11)), 21 CFR 58.53(b), 21 CFR 58.81 (by deletion of proposed 21 CFR 3e.81(b)(10)), and 21 CFR 58.120(a) (by deletion of proposed 21 CFR 3e.120(a)(17)). Reference to the regulations of the Nuclear Regulatory Commission has been removed from § 58.49; and proposed § 3e.115, dealing with the handling of carcinogenic substances, has been deleted. In addition, the Commissioner has deleted reference to the various animal care guideline cited in the proposal.

4. Some comments said the regulations should not be retroactive to previous studies or those ongoing and should include reasonable transitional provisions for their implementation.

To give nonclinical laboratory facilities adequate time to implement required changes in their organization and physical plant, a period of 180 days after publication in the FEDERAL REGISTER is provided for these regulations to become fully effective. The regulations are not retroactive. All studies initiated after the effective date shall be subject to the regulations. The remaining portions of studies in progress on the effective date of the regulations shall be conducted in accordance with these regulations.

5. A number of comments challenged the general legal authority of FDA to issue good laboratory practice regulations. Other comments challenged the legal authority to require record retention or quality assurance units, or to specify the content of required records or location of storage.

The Commissioner finds that the authority cited in the preamble to the proposal (41 FR 51219; Nov. 19, 1976) provides a sound legal basis for the regulations. Although many matters covered in these regulations are not explicitly mentioned in any of the laws administered by the Commissioner, the Supreme Court has recognized, in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973), that FDA has authority that "is implicit in the regulatory scheme, not spelled out *in haec verba*" in the statute. As stated in *Morrow* v. *Clayton*; 326 F.2d 36, 44 (10th Cir. 1963):

> However, it is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning* v. *Family Publications Service, Inc.*, 411 U.S. 356 (1973); see also *National Petroleum Refiners Association* v. *F.T.C.*, 482 F.2d 672 (D.C. Cir. 1973). The Commissioner concludes that there is ample authority for the promulgation of good laboratory practice regulations. No comment presented any explanation or information to the contrary, let alone a cogent argument that FDA lacks legal authority under existing statutes. The standards prescribed represent amplification of the legal requirements regarding evidence of safety necessary to approve an application for a research or marketing permit and parallel, to a great extent, steps that FDA has found have been taken by members of the regulated industry to improve nonclinical laboratory operations.

6. One comment argued that the opinion of the Court of Appeals in *American Pharmaceutical Association* v. *Weinberger*, 530 F.2d 1054 (D.C. Cir. 1976), should be read to limit FDA's authority to issue regulations under section 701(a) of the act (21 U.S.C. 371(a)).

The Commissioner disagrees with the argument advanced in the comment. As discussed in the preamble to the proposed regulation, the agency's authority to issue regulations under section 701(a) of the act has been upheld by the courts. (See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *National Confectioners Association* v. *Califano*, No. 76-1617 (D.C. Cir. Jan. 20, 1978); *Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).) The question is not FDA's authority to issue regulations under section 701(a) of the act per se, but whether regulations issued under section 701(a) of the act appropriately implement other sec-

tions of the act. As articulated in the original proposal, and as discussed in the previous two paragraphs, the Commissioner has determined that these regulations are essential to enforcement of the agency's responsibilities under sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act, as well as the responsibilities of FDA under sections 351 and 354-360F of the Public Health Service Act.

7. A number of comments said various sections of the act did not specify the submission of safety data or did not deal with "applications for research or marketing permits."

The Commissioner has reviewed the comments and finds that the comments are based on a misunderstanding of the phrase, "applications for research or marketing permits." This concept is discussed in relation to § 58.3(e) below. Each cited provision contains authority for FDA either to require submission of, or to use, nonclinical safety data to justify a decision to approve the distribution of a regulated product.

8. A number of comments said the cost of implementing the proposed regulations would be prohibitive to smaller testing laboratories and would, at the least, result in a substantial increase in the cost of product testing.

The Commissioner agrees that implementation of these regulations will increase the cost of nonclinical laboratory testing. The Commissioner finds, however, that such costs are justified on the basis of the resultant increase in the assurance of the quality and integrity of the safety data submitted to the agency. The agency has previously concluded (see the FEDERAL REGISTER of November 19, 1976 (41 FR 51220)) that this document does not contain regulations requiring preparation of an inflation impact statement under Executive Orders 11821 and 11929, Office of Management and Budget Circular A-107 and the guidelines issued by the Department of Health, Education, and Welfare. For a notice on the availability of the agency's economic impact assessment regarding rules for good laboratory practice for nonclinical laboratory studies, see the FEDERAL REGISTER of February 7, 1978 (43 FR 5071). The revisions in this final rule, along with the findings of the pilot program, which showed that many of the inspected facilities were already substantially in compliance with the proposed regulations, should allay some of the concerns of small facilities regarding cost or feasibility of compliance.

9. Many comments suggested changes in language, grammar, terminology, punctuation; sentence structure, and other editorial changes to clarify or improve upon the requirements as stated in the regulations or to eliminate redundancies or inconsistencies. Comments that raised significant policy questions, suggested changes in the substance of the regulation, or otherwise required, in the Commissioner's opinion, a specific response, are discussed individually below. Many of the suggested changes, however, were editorial and stylistic and do not warrant a detailed discussion.

The Commissioner has reviewed each of these numerous editorial and language changes to determine whether it offered an improvement in clarity or definition, eliminated an obvious error or redundancy, promoted consistency with other portions of the regulations, or otherwise identified textual problems that had not been previously noted by FDA. Where the proposed alternative language or other changes suggested by the comments were superior to the proposal, they were adopted in substance or verbatim. Where they did not offer any improvement, the Commissioner declined to accept them.

GENERAL PROVISIONS

SCOPE

10. Numerous comments addressed the stated scope of the proposed regulations (§ 58.1). Six comments said the proposed scope was vague. Ten comments said the scope should be limited to long-term animal toxicity studies. Twenty-two comments indicated that the scope should be limited to animal safety studies to be submitted to FDA. Individual comments recommended limiting the scope to studies performed on marketed products, studies performed on animals and other biological test systems, or studies submitted in support of a color additive petition, food additive petition, investigational new drug application, new drug application, or new animal drug application.

In the preamble to the proposed regulations, the Commissioner set forth the reasons for the broad terminology employed in the statement of scope, stating "these regulations are intended to ensure, as far as possible, the quality and integrity of test data that are submitted to FDA and become the basis for regulatory decisions made by the Agency." In the proposed rule (41 FR 51210), the Commissioner specifically invited comments on which laboratories and/or studies should be subject to the regulations, and further, on whether the scope of the regulations should be defined in terms of the type of testing facility rather than the type of study performed. Based on the review of the comments, the Commissioner has chosen to describe the scope of the regulations in language that is only slightly changed from the proposal. Further clarification of scope is achieved by the specific definition of the key terms, "nonclinical laboratory study" and "application for research or marketing permit" in § 58.3. Taken together, these provisions eliminate any vagueness in the scope of these regulations.

The Commissioner has rejected the request to narrow the scope by listing in the regulation specific types of studies covered. Any such list, if it included all types of studies used by the agency to assess the safety of all the products it regulates, would be cumbersome and might exclude specific types of studies that could become important to future safety decisions. The Commissioner emphasizes that this decision does not mean, however, that the scope of the regulations is unlimited. The scope of the GLP regulations is limited in several ways.

First, they apply only to nonclinical laboratory studies that are submitted or are conducted for submission to the agency in support of a research or marketing permit for a regulated product. Language has been added that provides that the scope includes studies "intended" to support applications for research or marketing permits. This language was included in the preamble to the proposed regulation (41 FR 51209), and the Commissioner has added the language to the regulation because it helps to make clear in advance when a study should comply with the regulation and when a study should be listed on a testing facility's master schedule sheet as a nonclinical laboratory study subject to these regulations (§ 58.35(b)(1)). Tests never intended to be submitted to the agency in support of (i.e., as the basis for) the approval of a research or marketing permit, such as exploratory safety studies and range-finding experiments, are not included even though they may be required to be submitted as part of an application or petition.

Second, the definition of "nonclinical laboratory study" (§ 58.3(d)) makes it very clear that studies utilizing human subjects, clinical studies, or field trials in animals are not included.

Third, the scope of coverage is now limited to safety studies, i.e., those which can be used to predict adverse effects of, and to establish safe use characteristics for, a regulated product. "Functionality studies" have been excluded in the final rule.

Fourth, the definition of "test system" (§ 58.3(i)) taken together with the definition of "nonclinical laboratory study" makes it clear that the scope of coverage is confined to studies performed on animals, plants, microorganisms or subparts thereof.

Products regulated by the agency, for which safety data may be required,

cover a wide range of diverse items that pose quite different types of risk. Examples include implantable medical devices; indirect food additives which may occur in food in very small quantities; direct food additives which may be consumed on a daily basis in larger quantities; human drugs intended for prescription or over-the-counter use; animal drugs intended for use in pets and other companion animals of social importance, drugs used in food-producing animals (drug residues can become a part of food); radiation products used in the diagnosis and/or treatment of a disease or condition; radiation products (e.g., microwave ovens and television sets) widely used by the public; vaccines; and blood components and derivatives.

The guarantee of the safety of each of these product classes requires conducting a broad spectrum of safety tests, all of which should be subject to the same standards. Therefore, the Commissioner rejects the proposal to limit the scope of these regulations to long-term animal toxicity studies. Median lethal dose (LD_{50}) and other short-term tests are covered by the regulations because they may serve as part of the basis for approval of, for example, use of an indirect food additive or an investigational new drug in man.

In vitro biological tests are included insofar as such tests have a bearing on product safety, even though they are not now used in agency decisions, because they may in the future become important indicators of safety. Examples of such tests include short-term mutagenicity tests as well as various other tissue culture and organ tests.

Also included in the scope of these regulations are studies of safety of regulated products on target animals, acute toxicity studies on a final product formulation, studies of test articles that are completed in 14 days or less, studies conducted on test articles used in "minor food producing species of animals," and studies on test articles which are not widely used.

11. Several comments closely related to the concerns expressed in paragraph 10 of this preamble requested that further language be added to the regulation exempting certain specific types of studies from coverage.

The Commissioner has reviewed the requests and has chosen not to change the language of the regulation itself to exclude specific study types other than those already mentioned (e.g., studies utilizing human subjects). The regulations apply to any study conducted to provide safety data in support of an application for a research or marketing permit for an FDA-regulated product, and a specific type of study which may be important in the overall safety evaluation of one type of regulated product may not be important in evaluating another. The Commissioner believes it useful to identify in this preamble further examples of studies that are—or are not—within the scope of the GLP regulations.

Examples of studies that are not within the scope of these GLP regulations include:

a. Clinical tests performed solely in conjunction with product efficacy.

b. Chemical assays for quality control.

c. Stability tests on finished dosage forms and products.

d. Tests for conformance to pharmacopeial standards.

e. Pharmacological and effectiveness studies.

f. Studies to develop new methodologies for toxicology experimentation.

g. Exploratory studies on viruses and cell biology.

h. Studies to develop methods of synthesis, analysis, mode of action, and formulation of test articles.

i. Studies relating to stability, identity, strength, quality, and purity of test articles and/or control articles that are covered by good manufacturing practice regulations.

Further examples of types of tests not covered include:

a. Food additives: Tests of functionality and/or appropriateness of the product for its intended use; tests of extractability of polymeric materials that contact food; and all chemical tests used to derive the specifications of the marketed product.

b. Human and animal drugs: Basic research; preliminary exploratory studies; pharmacology experiments; studies done to determine the physical and chemical characteristics of the test article independent of any test system; and clinical investigations.

c. Medical devices: All studies done on products that do not come in contact with or are not implanted in man.

d. Diagnostic products: Essentially all are excluded.

e. Radiation products: Chemical and physical tests.

f. Biological products: All tests conducted for the release of licensed biologicals described in Part 601 (21 CFR Part 601) of this chapter.

These examples do not represent all the exclusions from the regulations, but provide guidance in applying the agency's safety considerations to specific situations. The defined scope of the regulations is necessarily broad to encompass the wide range of types of safety tests, types of testing facilities and regulated products for which proper safety decisions are important.

12. More than 20 comments sought the addition of specific language exempting various classes of FDA-regulated products, such as medical devices, from coverage by the regulations.

The Commissioner has generally elected not to permit exemptions based on broad categories of regulated products because no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another. Proper safety decisions are important for all these products; accordingly, the processes by which such safety data are collected should be subjected to identical standards of quality and integrity.

13. Several comments said that the animal care provisions should apply only to these nonclinical studies using laboratory animals and should not apply to nonclinical studies which involve large animals.

It is clear that the animal care provisions are directed toward the use of laboratory animals, and therefore certain of these provisions may not apply to studies not involving laboratory animals, such as tissue residue and metabolism studies conducted in cattle. Although these studies do fall within the definition of a nonclinical laboratory study, the animals used in such a study are not generally kept in a laboratory setting. Because the husbandry requirements for laboratory animals differ greatly from those for large animals, the agency does not require that large animals be reared and maintained under the same conditions as laboratory animals. The regulations are revised to include terms such as "when applicable" and "as required" in those provisions for which a wide latitude of acceptable husbandry practice exists.

14. Three comments said the regulations should apply to all studies whether submitted in support of or as a challenge to an "application for a research or marketing permit."

The Commissioner agrees, in principle, that all nonclinical studies should be performed in a manner designed to ensure the quality and integrity of the data. FDA is requiring that, at the time a study is submitted, there be included with the study either a statement that the study was conducted in compliance with Part 58 requirements or, if the study was not conducted in compliance with those requirements, a statement that describes in detail all deviations. This requirement means that, at the time a study not conducted in compliance with the requirements is submitted, the agency may evaluate the effects of the noncompliance and take one of the following actions: (1) Determine that the noncompliance did not affect the validity of the study and accept it, or (2) determine that the noncompliance may have affected the validity of the study

and require that the study be validated by the person submitting it, or (3) reject the study completely. The standard of review applied to studies that contain data adverse to a product is no different. That is, a study that failed to comply with these regulations might, nonetheless, contain valid and significant data demonstrating a safety hazard. Thus, FDA is not proposing a double standard, but is, rather, seeking to address those studies that present the most serious regulatory problems.

The preamble to the proposed regulation (41 FR 51215) discussed this issue as follows:

> Valid data and information in an otherwise unacceptable study which are adverse to the product, however, may serve as the basis for regulatory action.
>
> This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard. It reflects current agency policy; even in situations where the scientific quality of an investigational drug study is not in question, FDA may receive data but not use it in support of a decision to approve testing or commercial distribution because of ethical improprieties in the conduct of the study. (See 21 CFR 312.20).

A positive finding of toxicity in the test system in a study not conducted in compliance with the good laboratory practice regulations, may provide a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that scientifically valid results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product. The treatment of studies conducted by a disqualified testing facility is discussed in paragraph 231a. below.

15. Exemptions from coverage by these regulations were requested for various types of facilities. Requests were received that they not apply to academic, medical, clinical, and not-for-profit institutions.

The public health purpose of these regulations applies to all laboratory studies on which FDA relies in evaluating the safety of regulated products, regardless of the nature of the facilities in which the studies are conducted. The Commissioner finds that granting an exemption based on type of facility would frustrate the intent of the good laboratory practice regulations. Many other comments urged that such exemptions not be considered because the standards applied to nonclinical testing should be uniform. Many of the requests for exemption were based on the idea that academic or not-for-profit institutions conduct primarily basic research and ought, therefore, to be specifically excluded. Insofar as academic institutions are concerned, the Commissioner notes that such institutions conduct significant amounts of commercial testing pursuant to contracts. He also notes that significant levels of noncompliance with GLP requirements have been found in such institutions. Moreover, as noted in paragraph 11, basic research on drugs is outside the scope of these regulations. In short, no justification has been presented to warrant granting an exemption to such a facility, and any such exemption from the regulations by the type of facility collecting safety data would not provide equal application of the principles of good laboratory practice. Product safety decisions are equally important whether data are collected by the largest commercial nonclinical laboratory facility or by the smallest nonprofit facility. Therefore, the data collected in all types of facilities should be subjected to the same standards of quality and integrity. The results of the pilot program show that the proposed regulations represent achievable standards.

16. Exemption of or different standards for studies conducted outside the United States were requested.

These regulations are designed to protect the public health of the American people by assuring the scientific integrity and validity of laboratory studies that the agency relies on in evaluating the safety of regulated products. The same assurance is needed, whether the studies relied on are foreign or domestic in origin. The Commissioner notes that FDA clearly may refuse to accept studies from any nonclinical testing facility, foreign or domestic, that does not follow the requirements set forth in these regulations. To exempt from the requirements imposed on studies conducted in domestic testing facilities a nonclinical study conducted in a testing facility outside the United States that is submitted to FDA in support of an application for a research or marketing permit or to impose different standards for such studies, would only have the effect of discriminating against U.S. firms. Although inspection of a foreign facility may not be made without the consent of that facility, FDA will refuse to accept any studies submitted by any facility that does not consent to inspection. These same conditions apply to other FDA regulations, e.g., the current good manufacturing practice regulations (21 CFR Part 210). a program of inspection of foreign facilities for compliance with those regulations has been conducted by FDA for several years. A similar inspection program of foreign laboratory facilities conducting studies within the scope of this regulation will be conducted; several foreign laboratories were inspected during the pilot program, and mechanisms for such inspections are being worked out with representatives of the responsible regulatory authorities in foreign countries.

DEFINITIONS

The Commissioner received hundreds of comments regarding definitions (§ 58.3). General comments are listed immediately below; comments regarding specific definitions follow in numerical order.

17. Several comments asked that commonly used terms such as "batch," "area," "laboratory," "pathologist," "quality data," "data integrity," "supervisor," and "management" be defined or clarified.

The Commissioner finds that, with the exception of "batch," the terms set out above do not require individual definitions. The term "pathologist" is used in its ordinary sense, as are the terms "supervisor" and "management" and the phrases "quality data" and "data integrity." As a general rule, the regulation defines separately only those words which will be used in a sense which differs from that given in currently accepted dictionaries or words whose meaning will be limited by the regulation. A new definition has been added for the term "batch" because it is used in these regulations in a context different from other agency regulations, e.g., the good manufacturing practice regulations. "Batch" in these regulations means a specific quantity of a test or control article that has been characterized according to § 58.105(a).

18. Several comments on § 58.3(b) questioned the applicability of the term "test substance" to medical devices, radiation products, in vitro diagnostic products, and botanical materials.

The Commissioner has reviewed the comments carefully and finds that many of the comments submitted regarding the term "test substance" argued that the term, as defined, did not accurately reflect the scope intended to be covered. Because the term "substance," in common usage, refers to chemical compounds and biological derivatives of more or less defined composition, and because the term is not commonly understood to include devices or electronic products, the Commissioner has changed the term "test substance" to "test article." The term "article" is intended to include all regulated products which may be the subject of an application for a research or marketing permit as defined in § 58.3(e).

The Commissioner has deleted the reference to botanical materials because all botanical materials subject to

FDA jurisdisction are adequately encompassed by the other articles specifically mentioned in the definition.

19. Clarification of the term "control substance" (§ 58.3(c)) was requested. Several comments asked whether the term was to include carrier substances and solvents and vehicles. Other comments sugested this term could be confused with the same term used by the Drug Enforcement Administration.

The term is changed to "control article" to parallel the revised definition for test article. This change avoids any potential conflict with definitions used by other agencies. The term is intended to define those materials given to control groups of test systems for establishing a basis of comparison. The Commissioner recognizes that for certain nonclinical laboratory studies, no control groups are used, and therefore this definition would not apply. For example, testing the safety of implantable pacemakers in animals would require either no control animals or animals that have only been "sham-operated." The definition includes carrier materials when such carrier materials are given to control groups within test system and likewise for administered vehicles and solvents. The term also applies to articles used as positive controls.

20. Many comments on § 58.3(d) addressed the definition of the term "nonclinical laboratory study." A great many, if not the majority, of the comments sought to change the definition by adding language excluding certain specific tests, products, or types of laboratories.

The Commissioner notes that many of these comments overlap with or are identical to comments submitted in response to § 58.1 (Scope). To the extent that the comments and issues are the same, they have been dealt with in the discussion of § 58.1, above. Other comments are dealt with specifically below.

21. Many comments stated that the proposed language which included studies intended to assess the functionality and/or effectiveness of a test article should be deleted. One comment stated that efficacy testing in nonclinical tests is, by definition, preliminary and should be excluded to be consistent with the scope defined in § 58.1. Other comments stated that the language was too broad and too ambiguous and could be interpreted to include many studies which were not safety studies at all.

The Commissioner has considered these comments and agrees that the language related to functionality and/or effectiveness is too broad. He has, therefore, deleted the sentence.

22. Several comments requested that the last sentence of § 58.3(d) be modified by deleting the proposed examples of tests.

The Commissioner finds that the examples included in the proposal tended to confuse rather than clarify. The examples, therefore, have been deleted.

23. Section 58.3(e), which defines the various types of submissions to FDA, was criticized for use of the term "application for research or marketing permit." Several comments said the term was misleading because not all products are regulated through the use of "permits."

The Commissioner believes the term is appropriate for the purpose of these regulations. As stated in the proposal, this definition includes all the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing marketing of a product. The term is intended solely as a shorthand way of referring to the separate categories of data (identified in the proposal) that are now, or in the near future will become, subject to requirements for submission to the agency.

24. One comment stated that proposed § 3e.3(e)(14) should be deleted because the language was overly broad and because it contradicted the intent expressed in the preamble to limit GLP regulations to safety studies.

The Commissioner notes that the preamble to the proposal (41 FR 51209) stated that studies conducted to determine whether a drug product conforms to applicable compendial and license standards were excluded from the regulation. Safety data submitted to obtain the initial licensing of a biological product are covered by these regulations in § 58.3(e)(13). Once a biological is licensed, however, it becomes subject to testing procedures similar to compendial testing procedures. The Commissioner finds that postlicensing testing of biologicals is conducted more for quality control purposes than for establishing the basic safety of the biologic product and has, accordingly, deleted postlicensing testing from the definition of research and marketing permit.

25. Several comments stated that in vitro diagnostic tests (proposed § 3e.3(e)(15)) should not be included because in vitro diagnostic products do not come in contact with patients and do not, therefore, require preliminary animal safety testing.

Because in vitro diagnostic products do not require any nonclinical laboratory tests for agency approval, the Commissioner agrees that in vitro diagnostic products need not be included in the definition "application for a research or marketing permit." Proposed § 3e.3(e)(15) has, therefore, been deleted from the final regulation.

26. Several comments objected to the inclusion of medical devices in § 58.3(e) (16), (17), and (18), stating that medical devices were not "test substances," that medical devices should not be included because the rules for data submission for such devices were as yet undefined, and that inclusion of medical devices would be unduly restrictive. These comments suggested either total or partial exclusion from coverage under the good laboratory practice regulations.

For reasons stated previously, the Commissioner does not agree that medical devices, as a category, should be excluded. Implantable devices may be composed of polymeric materials that contain components capable of leaching from the device into the body of the recipient or may themselves be adversely affected by body constituents. In either case, safety studies would be necessary to demonstrate that components of the device did not cause harm or that the body constituents did not promote breakdown or malfunction of the device.

27. Comments also requested deletion of all terms relating to radiation products in § 58.3(e) (20), (21), and (22), stating that to include such products would restrict experimentation unduly, and arguing that radiation products were not "test substances."

The Commissioner rejects these comments. The quality and integrity of the safety data are no less important for radiation products than they are for other agency-regulated products. He does not agree that including radiation products will unduly restrict experimentation. The remaining argument is covered in the discussion of "test article" above. A new paragraph § 58.3(e)(19) is added to cover data and information regarding an electronic product submitted as part of the procedure for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation performance standard, described in Subpart D of Part 1003 (21 CFR Part 1003).

28. Many comments stated that the term "sponsor" in § 58.3(f) was too broadly defined. For example, two comments stated that the definition, as written, would cover a company which provides a grant to a university, a fact which, if true, would inhibit giving grants. One comment said that the definition is so broad that it could be interpreted to apply to stockholders.

The Commissioner advises that a person providing a grant may be a sponsor. In the area of nonclinical laboratory studies, most grantors ulti-

mately submit the data to the agency. The Commissioner does not agree that because the definition of "sponsor" includes grantors it will inhibit the giving of grants. No data were submitted to support this argument. The Commissioner further advises that the definition does not include stockholders.

29. Other comments on § 58.3(f) asked whether the regulation allowed for multiple sponsors and whether government agencies could be sponsors.

"Person," as defined in § 58.3(h), includes government agencies, partnerships, and other establishments such as associations. Therefore, a government agency can clearly be a sponsor. In addition, the Commissioner advises that the definition does not preclude joint sponsorship of a study.

30. Several comments asked that the definition of "testing facility" in § 58.3(g) be revised to indicate clearly that a facility conducting a study subject to the regulations should be subject only to the extent that the facility is involved with and responsible for the study.

The Commissioner concludes that no revision to the definition is necessary. The definition clearly does indicate that a facility is covered by the regulations only to the extent that the facility is conducting or has conducted nonclinical laboratory studies.

31. Numerous comments addressed the definition of "test system" in § 58.3(i). Eighteen comments stated that the definition, as written, could be interpreted to require testing of beakers and test tubes. Two comments pointed out that the "test system" is not the container being tested for extractables, but rather it is the animal, microorganism, or cellular components used to test the extractables for safety.

The Commissioner has carefully reviewed the proposed definition in light of the comments and has made a number of changes. The terms "cellular and subcellular" have been replaced for clarity with "subparts thereof" which refers to animals, plants, and microorganisms. The revised definition now reads: "'Test system' means any animal, plant, microorganism, or subparts thereof, to which the test or control article is administered or added for study. 'Test system' also includes appropriate groups or components of the system not treated with the test or control articles." The revisions should make the definition clearly consistent with § 58.3(d) ("nonclinical laboratory study"), which states that studies to determine physical or chemical characteristics of a test article or to determine potential utility are not included. Therefore, testing of beakers and test tubes, which fall into the category of physical and chemical tests, is excluded.

32. Section 58.3(j), which defines "specimen," drew several comments. These included requests for precise definition of the terms "material" and "tissue" and requests for a clearer definition of the term "specimen."

The Commissioner is modifying the term "specimen" to include any material derived from a test system for examination or analysis. Under these circumstances, blood, serum, plasma, urine, tissues, and tissue fractions are all included if they are intended for further examination or analysis. The definition includes all materials that yield data related to the safety decision on a regulated product.

33. Many comments were received on the definition of "raw data" in § 58.3(k). Included were requests to clarify the term "certified" and to state whether carbons, photocopies, and written reports of dictated material could be classified as "raw data". Other issues concerned whether financial information and first drafts of reports were "raw data."

The Commissioner concludes that the proposed definition should be clarified. The word "exact" is substituted for the word "certified." "Certified" connotes a legal document that requires notarization; "exact" has no such connotation and more precisely reflects the Commissioner's intention. The definition is further clarified by inserting, after the first sentence, a new sentence which reads: "In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data." This clarification will permit data collection by tape recorders without requiring the retention of the original tapes. Carbons and photocopies satisfy the regulations, provided they are exact and legible copies of the original information. Neither financial information nor first drafts of reports are raw data within the meaning of the term.

34. Several comments said only recorded data contributing substantially to the study should be retained and, similarly, only computer printouts contributing substantially should be retained. Several comments requested clarification of the method for storing machine-generated data and definition of "on line data recording system."

Because the parenthetical example ("derived from on-line data recording systems") served more to confuse than to clarify, it has been deleted. However, an "on line data recording system" pertains to an instrument that can feed data directly into a computer that analyzes and stores the information. The product of this activity usually consists of a memory unit plus a computer program for extracting the information from the unit. Hard-copy computer printouts are unnecessary, provided the computer memory and program are accompanied by a procedure that precludes tampering with the stored information.

The Commissioner cannot agree that only those portions of the data that contribute substantially to the study need to be retained. Such an approach would require a judgment to be made which, if in error, could lead to improper or incorrect study reconstruction. The purpose of retaining the raw data is to permit the quality assurance unit and agency investigators to reconstruct each phase of a nonclinical laboratory study. Discarding essential records would frustrate this purpose. Raw data may be stored in separate areas provided the archival indexes give the data location.

35. Many comments addressed "quality assurance unit" in § 58.3(l).

The Commissioner has reviewed these comments and concludes that they are more concerned with the concept of the quality assurance unit than with the definition. The comments are therefore dealt with in detail in that section of the preamble concerned with § 58.35 of the regulations. (See paragraphs 75 through 92 below.)

36. Several comments addressed "study director" in § 58.3(m). These comments requested clarification, permission to have more than one study director per study, and that the term "implementation" be changed to "conduct."

The Commissioner has revised the definition to read: "'Study Director' means the individual responsible for the overall conduct of a nonclinical laboratory study." The revision is intended to emphasize that the study director is responsible for the entire study, as well as being responsible for the interpretation, analysis documentation, and reporting of results.

The Commissioner concludes that the other comments received on the definition of "study director" addressed the concept rather than the definition, and these comments are dealt with under the discussion of § 58.33 (see paragraphs 59 through 74, below).

APPLICABILITY TO STUDIES PERFORMED UNDER GRANTS AND CONTRACTS

37. Two comments requested revision of § 58.10 to specify clearly that the sponsor is ultimately responsible for data validity, even if the data are obtained by a sponsor from a grantee or contractor.

The Commissioner concludes that no revision of § 58.10 is necessary. All persons involved in a nonclinical laboratory study are responsible for part or all of the study, depending upon the extent of their participation. Athough a sponsor who submits studies to FDA bears the responsibility for the work performed by a subcontractor or grantee, that fact in no way relieves a grantee or subcontractor from individual responsibility for the portion of the study performed for the sponsor. Indeed, the purpose of the requirement that the sponsor notify a grantee or subcontractor that the work being performed is a part of a nonclinical laboratory study which must be conducted in compliance with the good laboratory practice regulations is to assure that all parties submitting data are aware of their responsibilities under the regulation.

38. Several comments requested exemption for certain specialized services which are not commonly available, e.g., ototoxicity studies with diuretics. The comments stated that these specialized services would probably not be available to them if the stringent requirements of the regulations had to be met by the service organization.

The Commissioner concludes that certain specialized services cannot be exempted from these regulations. The specialized services may contribute in large measure to the agency decision to approve a research or marketing permit. If the studies are intended to provide safety data in support of an application for a research or marketing permit, their conduct falls within the scope of these regulations.

INSPECTION OF A TESTING FACILITY

39. Comments on the inspection provisions (§ 58.15) expressed concern regarding the competence and scientific qualifications of FDA investigators.

The agency has endeavored, through a specialized training program, to assure that FDA investigators are competent to perform good laboratory practice inspections. The EILP program is new, and training and evaluation will continue to improve it. The results of the pilot inspection program and the manner in which it was coducted should provide added assurance to testing facility management regarding the competence of FDA investigators. The quality of the program is not, however, dependent on the competence or training of any single individual. Inspection of findings are always subject to supervisory review within the agency, and no official action may be taken without concurrence of a number of qualified persons.

40. Several comments stated that agency inspection should be limited to those facilities under current FDA legal authority.

The scope of the regulations and the definition of a "nonclinical laboratory study" define those studies covered by the regulations. The agency intends to inspect all facilities which are conducting such studies. Many of these facilities are subject to inspection under express statutory authority vested in FDA. As noted in the preamble to the proposal (41 FR 51220):

> Inspections of many, perhaps most, testing facilities will not be conditioned upon consent. Under section 704(a) of the act, FDA may inspect establishments including consulting laboratories, in which certain drugs and devices are processed or held, and may examine research data that would be subject to reporting and inspection pursuant to section 505 (i) or (j) or 507 (d) or (g) of the act. In addition, any establishment registered under section 510(h) of the Act is subject to inspection under section 704 of the act. Thus, most manufacturing firms that conduct in-house non-clinical laboratory studies on drugs and devices, and those contract laboratories working for such firms, would be subject to FDA inspection whether or not they consented.

Facilities that are not subject to statutory inspection provisions will be asked to consent to FDA inspection. The absence of any statutory authorization does not bar FDA from asking permission to conduct an inspection, and the agency should not bar itself from seeking permission. Thus, the proposal in the comment is not accepted.

41. Several comments requested that FDA make its enforcement strategy known as promised in the preamble to the proposal.

The enforcement strategy was discussed in the preamble to the proposal (41 FR 51216) and is amplified in the compliance program which implements this regulation. The compliance program is publicly available and may be obtained by sending a written request to the agency official whose name and address appear at the beginning of this preamble as the contact for further information.

42. Two comments on § 58.15 as proposed requested that the requirement that the testing facility permit inspection by the sponsor be deleted. The comments argued that the rights and obligations of a sponsor and its laboratory are a matter of contract between them alone, and not a proper subject for government regulation.

The Commissioner has considered this issue, is persuaded that the comments are correct, and has deleted the phrase "the sponsor of a nonclinical laboratory study." At the same time, however, the Commissioner reemphasizes that, because a sponsor is responsible for the data he or she submits to the agency, the sponsor may well wish to assure that the right to inspect a testing facility is included in any contract.

43. Other comments suggested that the sponsor should accompany the FDA investigator during an inspection of a contract testing facility and that FDA access to data should require the sponsor's consent.

The Commissioner disagrees with these comments. An agency investigator may be inspecting the results of studies from several sponsors during an inspection. The logistics required to notify and arrange for several sponsors to accompany an investigator, or to obtain sponsor consent to information release, would be unworkable. FDA's practice of unannounced inspections has proved to be an effective and efficient use of scarce resources. Because of resource limitations, FDA cannot inspect each facility as often as it would like to, and the Commissioner finds that the possibility of unannounced FDA inspections at any time motivates compliance.

44. Many comments were concerned that trade secret information obtained during the inspection would be released by FDA.

The Commissioner notes that trade secrets obtained as a result of an inspection are fully protected under the provisions of section 301(j) of the act (21 U.S.C. 331(j)), as well as 18 U.S.C. 1905 and the Freedom of Information Act (5 U.S.C. 552(b)(4)) and the FDA's implementing regulations (21 CFR 20.61). Interested parties may refer to the agency's public information regulations (21 CFR Part 20), which govern agency release of documents.

45. One comment requested that the results of government laboratory inspections be made public.

The Commissioner notes that no distinctions will be made between government or nongovernment laboratories. The results of an inspection of testing facilities will be available after all required followup regulatory action has been completed.

46. The phrase "and specimens" has been added to § 58.15(a). The Commissioner finds that examination of specimens may be required to enable the agency, where necessary, to reconstruct a study from the study records.

47. Many comments stated that the inspection of records should not extend to certain records compiled by the quality assurance unit.

The Commissioner agrees and has exempted from routine inspection those records of the quality assurance unit which state findings, note problems, make recommendations, or evaluate actions taken following recommendations. These exemptions from inspection are discussed in greater detail under the discussion of § 58.35.

48. A new paragraph (b) has been added to § 58.15. This paragraph is similar to proposed § 58.200 and reiterates that a determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not relieve an applicant from any obligation under any applicable statute or regulation (e.g., 21 CFR Parts 312, 314, 514, etc.) to submit the results to FDA. If a testing facility refuses inspection of a study, FDA will refuse to consider the study in support of an application for a research or marketing permit. This refusal, however, does not relieve the sponsor from any other applicable regulatory requirement that the study be submitted.

ORGANIZATION AND PERSONNEL

PERSONNEL

49. A number of comments addressed the definition of training, education, and experience in § 58.29. Several comments considered such references too vague; several others suggested that appropriate qualifications be established by professional peer groups.

It would be inappropriate, if not impossible, for FDA to specify exactly what scientific disciplines, education, training, or expertise best suit a specific nonclinical laboratory study. These factors, which vary from study to study, are left to the discretion of responsible management and study directors. They are responsible for personnel selection and for the quality and integrity of the data these personnel will collect, analyze, document, and report. The Commissioner urges, however, that management and study directors carefully consider personnel qualifications as they relate to a particular study. The agency has uncovered instances, discussed in the preamble of the proposal (41 FR 51207), in which the conduct of a study by inadequately trained personnel resulted in invalid data. Although the Commissioner recognizes the value of certification by professional peer groups, he does not agree that the concept is appropriate for regulatory purposes.

50. Several comments said the study director should be given responsibility for assurance of qualifications of personnel.

The Commissioner agrees that, generally, the study director will be responsible for ensuring that personnel selected to conduct a nonclinical laboratory study meet necessary educational, training, and experience requirements. The Commissioner notes, however, that management also has selection and hiring responsibilities and privileges.

51. One comment stated that the requirement of § 58.29 that each individual engaged in the conduct of a study have sufficient training or experience to enable the individual to perform the assigned function should be limited to those personnel engaged in supervision and collection and analysis of data.

The Commissioner disagrees. These factors are important and should be considered for personnel other than supervisors or those engaged in collection and analysis of data. The approach suggested by the comment would ignore the fact that specific expertise is required, for example, by animal caretakers, physical science technicians, and by persons using pesticides near animal-holding areas. While the degree of education, training, and experience necessary for these positions will be quite different from the qualifications necessary for supervisors or scientific staff, the need for sufficient training or experience is no less important.

52. One comment pointed out the appropriateness of changing the term "person" to "individual" in § 58.29(a).

Because the term "person" as defined in § 58.3(h) includes partnerships, corporations, etc., the Commissioner agrees that "individual" is the proper term and has so amended § 58.29(a).

53. Seventeen comments questioned the use of, or objected to reference to, the term "curriculum vitae" for nontechnical personnel such as animal caretakers, as required in proposed § 58.29(b).

Another comment asserted that the requirement infringed on management's prerogatives without specifying how any such infringement occurred. One comment stated that the requirement that such records be retained after termination of employment was unnecessarily cumbersome.

The Commissioner does not agree that the requirement infringes on management's prerogatives. However, the Commissioner agrees with the remaining comments and has revised the section. "Curriculum vitae" has been changed to "summaries of training and experience plus job descriptions." Reference to the maintenance of records of terminated employees is deleted from this section because the requirement is redundant to the record retention requirements set forth in § 58.195(e).

54. Ten comments said the wording of § 58.29(c), relating to "sufficient numbers of personnel" and to "timely" conduct of the study, was vague.

The Commissioner purposely left the paragraph broad in context and coverage because differences in types of studies preclude any specific approach to defining numbers of personnel. The precise number of personnel reuired for a specific study, as well as for all ongoing studies, is a management decision. FDA experience, however, indicates that a shortage of qualified personnel can lead to inadequate or incomplete monitoring of a study and to delayed preparation and analysis of results, and the numbers of personnel conducting a study should be sufficient to avoid these problems.

55. Ten comments requested deletion of § 58.29(d) or clarification of the language regarding employee health habits, stating that the section was too vague and that an employer was responsible for health habits only at work. One comment submitted alternate language.

The Commissioner adopts with modifications the alternate language. The paragraph now requires only that personnel take necessary personal sanitation and health precautions to avoid contamination of test and control articles and test systems.

56. Several comments asked that the term "laboratory" in § 58.29(e), as applied to protective clothing, be deleted because it is too restrictive. Other comments suggested that the requirement that clothing be changed as often as necessary to prevent contamination be eased by changing "prevent" to "help prevent." Four related comments requested modification to reflect only "contamination affecting validity of studies."

The Commissioner agrees to the elimination of "laboratory" as applied to clothing. The provision of specialized clothing is, however, an estalished and well-known procedure for preventing contamination in a variety of situations. The Commissioner disagrees with any suggested modification of this section which weakens the intent of the regulation. The objective is to prevent contamination of the test system.

57. A number of comments addressed several aspects of § 58.29(f) regarding personal illnesses, personal health records, types of illnesses, and records of illnesses. Comments said disclosure of medical records was an invasion of privacy and of little relevance to the proper conduct of a nonclinical laboratory study.

The Commissioner agrees that documentation of personal illnesses may constitute an unwarranted invasion of privacy, and this requirement is deleted. The Commissioner disagrees with the requests for deletion of the entire paragraph, noting the relationship between personnel health and possible contamination of test systems. Revised § 58.29(f) requires individuals with illnesses that may adversely affect the quality and integrity of nonclinical laboratory studies to be excluded from direct contact with test and control articles and test systems.

The Commissioner has deleted from § 58.35(a) the sentence in question. The QAU of the testing facility is solely responsible for fulfilling the quality assurance functions for studies conducted within that facility. In those cases where portions of a study, e.g., feed analysis, are performed by a contract facility which, because it is not itself a nonclincial facility, does not have a QAU, the person letting the contract, and not the contract facility, is responsible for the performance of the quality assurance functions.

The Commissioner believes that the mechanism by which a sponsor is assured of the quality of nonclinical studies performed for it under contract is a matter that can be left to the contracting parties and need not be addressed in these regulations.

80. Three comments suggested that testing facilities be licensed or certified in lieu of having an ongoing quality assurance unit.

The Commissioner considered such an approach and rejected it before publishing the proposed regulations. (See 41 FR 51208-51209.) No persuasive arguments for changing this decision were presented in the comments. The diversity in the size and nature of nonclinical testing facilities subject to the provisions of these regulations makes licensing or certification procedures impractical. The regulation is intended to assure the quality and validity of the data obtained by each nonclinical laboratory study, and the QAU provides a mechanism to monitor each ongoing study. Licensing a testing facility could not achieve the same result.

81. Many comments objected to the provisions of § 58.35(b)(1) which require that the quality assurance unit maintain a master schedule sheet of all nonclinical laboratory studies. Some comments believed the requirement was excessive, while others questioned the proposed format and contents of the list. One comment pointed out that not every study includes all items listed.

The Commissioner is convinced that maintenance of a master schedule sheet is essential to the proper function of the Quality Assurance Unit. Only through such a mechanism can management be assured that the facilities are adequate and that there are sufficient numbers of qualified personnel available to accomplish the protocols of all nonclinical studies being conducted at a facility at any given time.

Upon careful review of the items required to be listed, the Commissioner agrees that the requirement that animal species be identified may be deleted because the requirement that "test system" be listed adequately covers this point. He has, in addition, deleted the examples of study types because he agrees that including the information is not necessary to achieve objectives of this section. The Commissioner has further reworded this section to eliminate reference to whether the final report has been approved for submission to the sponsor because the language was strictly applicable only to studies done under contract. The revised language simply requires that the status of the final report be listed.

82. Nine comments objected that § 58.35(b)(2) required too much duplicative paper.

The Commissioner has concluded that the QAU must maintain copies of study protocols to assure that they are followed and amended in accordance with the further provisions of these regulations. The Commissioner agrees that the requirement that the QAU maintain copies of all standard operating procedures would substantially increase the volume of records needed to be retained by this unit. Because there should be many copies of standard operating procedures present throughout the facility which should be freely available to QAU members, the Commissioner has deleted the requirement that these be maintained by the QAU.

83. Fifteen comments suggested that § 58.35(b)(3) be deleted on the basis that FDA should not dictate how the QAU achieves its objectives. One comment suggested that "inspect" be changed to "audit."

The Commissioner remains convinced of the need for a formal mechanism through which the QAU maintains oversight of the conduct of a study. Such a mechanism must be based on direct observation in order that the independence of the QAU be preserved. The Commissioner has retained the word "inspect" in preference to "audit." "Inspect" more accurately conveys the intent that the QAU actually examine and observe the facilities and operations for a given study while the study is in progress, whereas "audit" could be interpreted to mean simply a detailed review of the records of a study. Because the QAU function is to observe and report the state of compliance with the regulations and to determine whether the protocol is being followed rather than to verify the results of a study, "inspect" more properly conveys the agency's intent.

84. Fourteen comments addressed the need to inspect "each phase of a study * * * periodically," seeking clarification or different language. Nine of these comments called for the use of random sampling procedures in choosing studies or phases of studies to inspect in order to decrease the workload and resource requirements of the QAU.

The Commissioner does not agree that random sampling would be an adequate method of evaluation in the nonclinical laboratory setting. In situations which involve the repetition of similar or identical procedures, random sampling can provide an adequate means of quality control. Here, however, the differences among study operations and among the personnel conducting them invalidate any assumption that the conduct of one phase of one study is representative of the conduct of that phase of another or of other phases of a single study. The term "each phase" is intended to emphasize the need for repeated surveillance at different times during the conduct of a study so that each critical operation is observed at least once in the course of the study. The term "periodically" is retained to indicate the need for more than one inspection of certain repetitive continuing operations that are part of the conduct of longer term studies such as animal observations and diet preparation.

85. Many comments objected to the proposed requirement that any problems found by the QAU be brought to the attention of management and appropriate responsible scientists. Some felt that this would require that excessive resources be spent on minor problems. Others felt that notification of appropriate supervisory personnel rather than management was sufficient.

The Commissioner agrees that only those problems likely to affect the outcome of the study need to be brought to the immediate attention of personnel who are in a position to resolve those problems, and the language of § 58.35(b)(3) has been changed accordingly. The term "management" in its ordinary usage means appropriate supervisory personnel and has not, therefore, been changed.

86. More than 40 responses to proposed § 3e.33(b)(4) objected to the specific time frames required for evaluation. Several comments suggested that the paragraph be deleted. Others objected to the specific requirements, and still others stated that appropriate times for evaluatuations should be selected by management.

The Commissioner advises that periodic inspection is necessary and that the time periods specified are the minimum required to assure that a study is being conducted in compliance with the regulation. Should deviations be found during the periodic inspections, there may still be time to take corrective action. The Commissioner has, however, determined that inspection of studies lasting less than 6 months need only be conducted at intervals adequate to assure the integri-

ty of the study and that specific time intervals for such studies need not be set out in this regulation. The requirement that studies lasting more than 6 months be inspected every 3 months remains unchanged. The section has been added to § 58.35(b)(3).

87. Several comments requested that the phrase "complete evaluation" in proposed § 3e.33(b)(4) be clarified.

The Commissioner has changed the term "complete evaluation" to "inspect." The function of the QAU is to inspect studies at specified intervals to maintain records required by this regulation, and to report to management and the study director deviations from the protocol and from acceptable laboratory practice. Evaluation of any reported deviations is left to the study director and to management.

88. Fifteen comments sought deletion of § 58.35(b)(4), which requires the periodic submission of status reports to management and the study director. Three comments questioned the need to note problems and corrective action taken.

The Commissioner has retained this provision as proposed. Only through the submission of such status reports can management be assured of the continuing conformity of study conduct to the provisions of these regulations. Because § 58.35(b)(3) has been revised to require that only significant problems be reported immediately to management, the periodic status report becomes even more important as a means of informing management of minor problems and normal study progress. The status reports are needed to document problems and corrective actions taken so that management can be certain that quality is being maintained and that management intervention is not required. The timing of such reports may be determined by management.

89. Six comments objected that the term "prior" preceding "authorization" in § 58.35(b)(5) was too restrictive. The comments pointed out that unforeseen circumstances may prevent prior authorization for deviations from standard procedure and that the QAU should be concerned with the documentation of the deviation, not with whether prior authorization existed. Two comments stated that the QAU cannot assure that deviations do not occur but can determine, by inspection, whether deviations were documented.

The Commissioner is persuaded that prior authorization cannot always be obtained. For example, a fire in the facility would necessitate immediate action. The Commissioner agrees that documentation of the deviation rather than prior authorization is the important point and has deleted "prior" and added "documentation." In addition, "assure" has been changed to "determine" to respond to the comments and to reflect more accurately the Commissioner's intent. Section 58.35(b)(5) now reads: "Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation."

90. Several comments objected to the wording of § 58.35(b)(6), which states that the QAU shall review the final study report. The comments stated that such review requires a scientific judgment and is not an appropriate function for the QAU to perform. One comment suggested that the requirement should be modified to allow for random sampling rather than a complete review of all studies.

The Commissioner agrees that the QAU should not attempt to evaluate the scientific merits of the final report. Therefore, he has modified the paragraph. The QAU must however ensure that the final report was derived from data obtained in accordance with the protocol. Data in the final report significantly contributing to the quality and integrity of a nonclinical laboratory study shall be reviewed. A random sampling approach is not acceptable.

90a. The Commissioner has added to § 58.35 new paragraph (b)(7) which requires that the QAU prepare and sign a statement to be included with the final report which specifies that dates inspections of the study were made and findings reported to management and the study director. This requirement clarifies the fact that QAU review should extend through the completion of the final report and provides a mechanism for documenting that the review has been completed. A conforming section has been added to the final report requirements of § 58.185 as new paragraph (a)(14).

91. Many comments argued that requiring all portions of a quality assurance inspection to be available for FDA inspection might serve to negate their value as an effective management tool for ensuring the quality of the studies during the time in which the studies are being conducted.

The Commissioner shares the concerns of the comments that general FDA access to QAU inspection reports would tend to weaken the inspection system. He believes that FDA's review of quality assurance programs is important, and he recognizes the need to maintain a degree of confidentiality if QAU inspections are to be complete and candid. Therefore, the Commissioner has decided that, as a matter of administrative policy, FDA will not request inspections and copying of either records of findings and problems or records of corrective actions recommended and taken; and §§ 58.15 and 58.35(c) have been revised to separate those records subject to regular inspection by FDA from those records not subject to such inspection. Exempt from routine FDA inspection are records of findings and problems as well as records of corrective actions recommended and taken. All other records are available. Although the Commissioner is deleting the requirement in new § 58.35(d) that testing facility management shall, upon request by an authorized employee, certify in writing that the inspections are being performed and that recommended action is being or has been taken. Upon receiving such a request, management is required to submit the certification of compliance. A person who submits a false certification is liable to prosecution under 18 U.S.C. 1001.

The one exception to FDA's policy of not seeking access to records of findings and problems or of corrective actions recommended and taken is that FDA may seek production of these reports in litigation under applicable procedural rules, as for otherwise confidential documents.

92. Many comments objected that requiring internal quality assurance audits to be available to the agency might violate the constitutional privilege against compelled self-incrimination.

The Commissioner disagrees with the comments. It is settled that the privilege against compelled self-incrimination is an individual privilege relating to personal matters; the privilege is not available to a collective entity, such as a business enterprise, or to an individual acting in a representative capacity on behalf of a collective entity. *California Bankers Ass'n* v. *Schultz*, 416 U.S. 21, 55 (1974); *Bellis* v. *United States*, 417 U.S. 85 (1974); *United States* v. *Kordel*, 397 U.S. 1, 8 (1970); *Curcio* v. *United States*, 354 U.S. 118, 122 (1957); *United States* v. *White*, 322 U.S. 694, 699 (1944); *Wilson* v. *United States*, 221 U.S. 361, 382-384 (1911); *Hale* v. *Henkel*, 201 U.S. 43, 74-75 (1906). Even for individuals, the privilege against compelled self-incrimination is inapplicable where a reporting requirement is applied to an "essentially noncriminal and regulatory area of inquiry," where self-reporting is the only feasible means of securing the required information, and where the requirement is not applied to a "highly selective group inherently suspect of criminal activities" in an "area permeated with criminal statutes." *California* v. *Byers*, 402 U.S. 424, 430 (1971); *Marchetti* v. *United States*, 390 U.S. 39 (1968); *Albertson* v. *SACB*, 382 U.S. 70, 79 (1965); *Shapiro* v. *United States*, 335 U.S. 1 (1948).

ACCESS TO PROFESSIONAL ASSISTANCE

93. Comments on proposed § 3e.35 suggested rephrasing the statement to specify that professional assistance be authorized by the study director, that it be either in person or by telephone, that it be available within a reasonable period, and that reference to availability of a veterinary clinical pathologist be included. Other comments suggested that the concept was duplicative of the function of the study director and should be deleted.

The Commissioner proposed this requirement to assure that a scientist or other professional would be available to respond to requests for assistance or consultation from less experienced personnel. However, because management is responsible for assuring that personnel are available and that personnel clearly understand the functions they are to perform, and because the study director has overall responsibility for the technical conduct of the study, access to professional assistance is a matter best left to management's discretion. Therefore, the section is deleted from the final regulations.

FACILITIES

GENERAL

94. Many comments requested definition or clarification of the terms denoting separation (i.e., separate area, defined area, separate space, and specialized area), which are used in §§ 58.41, 58.43, 58.47, 58.49, and 58.90.

The Commissioner's intent in proposing that there be defined (and, where required, separate or specialized) areas in a testing facility was to assure the adequacy of the facility for conducting nonclinical laboratory studies. This intent is more clearly stated in the revised second sentence of § 58.41, which now reads: "It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study." The important point is that the facility be designed so that the quality and integrity of the study data is assured. The manner in which the separation is accomplished may be determined by testing facility management.

Adequate separation may be, in various situations, a function of such factors as intended use of the specific part of the facility, space, time, and controlled air. The broad variety of test systems, test and control articles, and the size and complexity of testing facilities preclude the establishment of specific criteria for each situation. For these reasons the Commissioner declines to include in the regulation either a definition or specific examples of methods for achieving adequate separation.

95. One comment suggested that a number of additional animal care and facility requirements be added to the regulations. The suggestions included, e.g., ambience to assure nonstressful conditions; ventilation and room access arranged to prevent cross contamination; and surveillance of animal health before and during a test or experiment.

The Commissioner concludes that no additional requirements need to be added because the regulation, as it stands, adequately covers the additions proposed by the comments. For example, ventilation and room access arranged to prevent cross contamination are addressed by the degree of separation requirement in § 58.41.

ANIMAL CARE FACILITIES

96. Many comments suggested that accreditation of animal care facilities by a recognized organization should provide adequate evidence that a testing facility is in compliance with § 58.43(a). One comment suggested accreditation by recognized organizations for analytical laboratories.

Although the Commissioner is aware of the value of accreditation programs, he cannot delegate FDA's responsibility for determining compliance with these regulations to an organization over which FDA has no authority. Few, if any, accreditation programs cover the same areas covered by this regulation. Furthermore, the Commissioner is unaware of any facility accreditation program which is mandatory. The agency's obligation to inspect a testing facility for overall compliance would not be altered by the fact that a facility was otherwise accredited.

97. Numerous comments objected to the requirements concerning separation of species, isolation of projects, and quarantine of animals as impractical and not necessary in all instances, e.g., separation of species in large animal studies and quarantine of all newly acquired animals. Some of the comments stated that the requirements of this section allow no latitude for judgment concerning their applicability.

The Commissioner reiterates that all requirements may not be applicable or necessary in all nonclinical laboratory studies and that the degree to which each requirement should apply in each case can be determined by informed judgment. Because of the variability of nonclinical laboratory studies, a degree of flexibility in applying the requirements of § 58.43(a) is necessary, and the language of § 58.43(a) is amended to read: "A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals." As noted in the general discussion at the beginning of this preamble, all references to other standards ("The Animal Welfare Act") have been deleted.

98. Several comments suggested that § 58.43(b) be amended to include isolaton of test systems with infectious diseases as well as isolating studies conducted with infectious or otherwise harmful test articles.

The Commissioner agrees that test systems with infectious diseases should be isolated. Proposed § 3e.49(b) provided for specialized areas for handling volatile agents and hazardous aerosols. Section 3e.49(b) also provided for special procedures for handling other biohazardous materials. Proposed § 3e.49(c) provided for special facilities or areas for handling radioactive materials.

To clarify all these requirements, the Commissioner has amended § 58.43(b) to read: "A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents." The provisions in proposed § 3e.49(b) and (c) regarding specialized areas for handling volatile agents, hazardous materials and radioactive materials are deleted from § 58.49.

99. One comment on § 58.43(c) suggested that, in addition to the area designated for the care and treatment of diseased animals, a separate area should be provided for animals with contagious diseases.

The Commissioner agrees, and the paragraph is amended to allow for an area for treatment of animals with contagious diseases, and it is to be separate from the area designated for the care and treatment of diseased animals.

100. Several comments questioned the requirement for separate areas for diseased animals, indicating that often such animals are sacrificed rather than treated.

The Commissioner does not agree that a separate area is not always needed for diseased animals. Although diseased animals may be sacrificed, this is not always the case, and it may not always be possible immediately to sacrifice diseased animals. Thus, a separate area should be available for such animals until sacrifice can be accomplished.

101. One comment requested that § 58.43(e), which deals with facility design, construction, and location to minimize disturbances that interfere with the study, should also define the

acoustic and sound-insulating requirements necessary to satisfy this requirement.

The Commissioner concludes that it is impractical to attempt to define acoustic and sound insulation requirements. It would be equally impractical to attempt to define all other types of possible disturbances that might interfere with a study.

ANIMAL SUPPLY FACILITIES

102. One comment asked that § 58.45 be clarified by specifically excluding "carriers" from the storage requirements.

The term "carrier," as used in § 58.113, is the material with which the test article is mixed, e.g., feed. The Commissioner concludes that it is necessary to provide facilities for proper storage of carriers and declines, therefore, to exclude them from the storage requirements.

103. One comment requested deletion of the section, stating that it discusses items not appropriate for FDA concern.

Improper storage of feed, carriers, bedding, supplies, and equipment can adversely affect the results of a study. Therefore, the Commissioner finds these matters to be of legitimate concern to FDA and declines to delete the section.

104. Two comments stated that separate storage space need not be required as long as material is properly stored and does not interfere with the conduct of the study.

The Commissioner agrees with these comments, in principle, but is convinced that storage areas for feed and bedding should be separate from the areas housing the test system to preclude mixups and contamination of the test systems. The section has been modified by adding the words "as needed."

FACILITIES FOR HANDLING TEST AND CONTROL ARTICLES

105. One comment stated that § 58.47, as worded, represented an impossible standard and suggested that use of the "designed to prevent" concept would be more realistic.

The Commissioner rejects this comment. The inherent purpose or "design" of all regulations is to prevent or require some action, and the use of the phrase "designed to prevent" would be an awkward and ambiguous modification of § 58.47.

106. Numerous comments objected to creating the number of separate or defined areas proposed by § 58.47, stating that the volume of testing would make it infeasible to create all the separate areas. One comment asked whether eight separate areas were required.

The Commissioner reiterates that the purpose of this section is to assure that there exists a degree of separation that will prevent any one function or activity from having an adverse effect on the study as a whole. Because of the wide variety of studies covered by these regulations, a degree of flexibility is appropriate in applying these requirements, and the degree to which each requirement should apply in each case may vary. To make this clear, the term "defined" has been deleted from § 58.47. Section 58.47(a) now reads: "As necessary to prevent contamination or mixups, there shall be separate areas for * * *." There is no specific requirement for eight separate areas.

LABORATORY OPERATION AREAS

107. A number of comments stated that § 58.49 required clarification, that in some instances more than one activity could be permitted in the same room, and that certain of the requirements would not be appropriate in every case.

The Commissioner agrees that the section as proposed was subject to misinterpretation. Because of the nature and scope of the types of studies subject to these regulations, it would be inappropriate to set specific uniform requirements for all studies. Therefore, the provisions are revised to make it clear that reasonable judgments regarding area and space requirements may be made on the basis that a particular function or activity will not adversely affect other studies in progress. Proposed § 58.49(b) has been revised, and the references to biohazardous materials has been added to the list of activities in § 58.49(a). (See the discussion at paragraph 98 above.)

108. Two comments suggested that the wording of § 58.49(a) be changed to refer to "adequate" rather than "separate" laboratory facilities, stating that animal studies require that laboratory facilities be available on the immediate premises. One comment requested that provisions be made for the use of outside laboratory facilities.

The Commissioner concludes that the term "separate" is proper in the context of § 58.49(a). He does not agree that laboratory facilities must be available on the immediate premises of the testing facility, and finds that many laboratory functions can be conducted properly in separate buildings or by independent laboratories located outside the testing facility.

109. Two comments on § 58.49(b) stated that the requirement that space and facilities separate from the housing areas for the test systems be provided for cleaning, sterilizing, and maintaining equipment and that supplies should apply only to major equipment.

The Commissioner does not agree. The objective of the requirement is to prevent the occurrence of those adverse effects which might result to a study from the activities of cleaning, sterilizing, and maintaining. No meaningful distinctions based on "major" or "not major" equipment can be made.

110. One comment on § 58.49(b) stated that the proposed wording did not have useful application in all test systems or studies and that the section should be rewritten to focus on the intended principle and not on the way to achieve it.

The section has been revised. It now reads, "separate space shall be provided for cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study." The revised wording grants flexibility in application as long as study results are not affected.

SPECIMEN AND DATA STORAGE FACILITIES

111. Several comments asked whether § 58.51 applied to completed or ongoing studies. Concern was also expressed that limiting access to storage areas to authorized personnel was not feasible.

This section is amended to apply to archive storage of all raw data and specimens from completed studies. The commissioner cannot agree, however, that limiting access of the archives to authorized personnel only is not feasible. Prudence would dictate such limited access even in the absence of a requirement. The potential for misplaced data and specimens is too great to allow unlimited access to the archives.

ADMINISTRATIVE AND PERSONNEL FACILITIES

112. One comment on § 58.53(a) stated that the section was unnecessary because adminsitrative functions had been previously defined in §§ 58.29, 58.33, and 58.35.

The Commissioner notes that this section specifies facilities rather than duties. References to OSHA regulations have been deleted.

EQUIPMENT

EQUIPMENT DESIGN

113. Five comments on § 58.61 stated that the section was fragmented and redundant.

The Commissioner agrees with these comments and has consolidated the section into one paragraph, which reads: "Automatic, mechanical or electronic equipment used in the generation, measurement or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capac-

ity to function according to the protocol and shall be suitably located for operation, inspection, cleaning and maintenance." This consolidation eliminates the fragmentation and redundancy of the proposal and specifies clearly that the requirements are limited to that equipment which, if improperly designed, or inadequately cleaned and/or maintained, could adversely affect study results.

114. Two comments objected to the undefined general terms "adequate" and "appropriate" in § 58.61.

The Commissioner points out that broad terms are necessary because of the wide range of equipment used in the studies covered. Exact design and capacity requirements for each piece of equipment are clearly beyond the scope of these regulations.

115. Four comments on § 58.61 stated that how cleaning is accomplished is irrelevant and that the regulation should emphasize accomplishment rather than ease of accomplishment.

The Commissioner agrees that the primary concern is that adequate cleaning be accomplished. However, past experience has demonstrated that when equipment is not designed and located to facilitate cleaning and maintenance, it is much less likely to be adequately cleaned and maintained.

MAINTENANCE AND CALIBRATION OF EQUIPMENT

116. Five comments suggested that § 58.63(a) should allow the required functions to be performed at the time the equipment is used rather than specifying that the functions be performed regularly.

The Commissioner agrees that performing these functions at the time of use is satisfactory and is amending § 58.63(a) to provide flexibility. The second sentence of this section now reads: "Equipment used for the generation of data shall be adequately tested, calibrated and/or standardized."

117. Two comments suggested that "calibrated" should be changed to "standardized" because the word "calibrated" normally means a performance check against known standards, whereas "standardized" normally means to make uniform.

The Commissioner finds that for some equipment the term "calibrated" is more appropriate and for other equipment the term "standardized" is more appropriate. Revised § 58.63(a) allows application of either term.

118. Two comments suggested that the reference to the use of cleaning and pest control materials is misplaced in § 58.63(a).

The Commissioner agrees that this use is more appropriately addressed under "Testing Facility Operations", and the requirements have been transferred to § 58.90(i).

119. Comments requested a precise definition of the equipment for which § 58.63(b) requires written standard operating procedures.

The Commissioner advises that because of the range of study and product types covered, such a list is impractical. The language of this section is retained as proposed to encompass the total range of equipment used in conducting nonclinical studies.

120. Eleven comments questioned the appropriateness of designating a responsible individual in § 58.63(b).

The Commissioner has changed "individual" to "person" as defined in § 58.3(h) to allow for designation of an organizational unit.

121. One comment indicated the need for a clear FDA policy regarding primary calibration standards.

The Commissioner concludes that proper standards are the responsibility of management, and these are to be set forth in the standard operating procedures.

122. One comment agreed with the standard operating procedure requirements of § 58.63(b), but suggested a several year phase-in period.

The Commissioner concludes that 180 days is a sufficient time period for developing standard operating procedures. Furthermore, the Commissioner's intent to require such procedures has been known since November 1976, when the proposed regulation was published.

123. Seven comments suggested that the manufacturer's recommendations should be sufficient for standard operating procedures. Additionally, one comment pointed out that maintenance could be subcontracted and a certificate should be allowed.

The Commissioner advises that the regulation does not preclude the use of manufacturer's recommendations as part of the standard operating procedures, nor does it preclude subcontracting maintenance. The Commissioner advises, however, that if a facility decides to subcontract maintenance, that fact does not relieve the facility of the responsibility for maintenance.

124. One comment argued that the requirement that all equipment records specify remedial action to be taken is excessive, and two comments said there are too many variables to specify in advance the remedial action to be taken.

The Commissioner notes that trouble-shooting charts are available for most equipment. The remedial action taken may influence the results of the study and therefore must be documented.

125. Several comments suggested that the equipment for which standard operating procedures are required be limited by rewording in one of the following ways: "major" equipment, "equipment used in data collection," or "delicate, complex equipment."

The Commissioner has considered the comments and has modified the language of § 58.63(b) to require that standard operating procedures describe in "sufficient" detail the procedures to be used in cleaning, testing, and standardizing equipment. The Commissioner points out that § 58.81(a) (standard operating procedures) states that the written standard operating procedures are to be those which management is satisfied are adequate to ensure the quality and integrity of study data. While the Commissioner does not find it feasible to confine the requirement for standard operating procedures to "major" equipment, he does find that the regulation clearly contemplates that the required procedures need be only as detailed as deemed necessary to assure the integrity of the study data. Simple equipment, therefore, should require only brief standard operating procedures.

126. Five comments suggested that written records for nonroutine repairs should only be required where the nature of the malfunction could affect the validity and integrity of the data.

The Commissioner rejects this suggestion because it is not always possible to make this judgment ahead of time.

127. Many comments argued that the recordkeeping requirements of § 58.63(c) are excessive.

The Commissioner has concluded that the cost of maintaining records of cleaning exceeds the benefits, and this requirement is deleted. However, the requirement for maintaining records of all inspections, maintenance, testing, calibrating and/or standardizing operations is retained because these records may be necessary to reconstruct a study and to assure the validity and integrity of the data.

128. One comment proposed that a new sentence, reading as follows, be added to § 58.63(c): "Where appropriate, the written record noted above may consist of a notation temporarily fastened to the piece of equipment stating when the last specified action with respect to the equipment was taken."

The Commissioner finds that the suggested approach is not precluded by the language of the section as written, but cautions that where such an approach is used, the notations constitute records which must be retained as required by § 58.195(f).

129. One comment asked whether each client of a contract facility must receive a copy of the equipment maintenance and calibration records.

The Commissioner concludes that the regulation does not so require.

TESTING FACILITIES OPERATION

STANDARD OPERATING PROCEDURES

130. Two comments suggested deleting § 58.81 in whole or in part. Several others said the requirements for standard operating procedures were unnecessary and burdensome.

The Commissioner does not agree. The use of standard operating procedures is necessary to ensure that all personnel associated with a nonclinical laboratory study will be familiar with and use the same procedures. These requirements will prevent the introduction of systematic error in the generation, collection, and reporting of data, and they will ensure the quality and integrity of test data that are submitted to FDA to become the basis for decisions made by the agency. The Commissioner recognizes that the requirements for standard operating procedures may place an additional burden on testing facilities, but finds that the resulting benefits should outweigh the burden. The requirements will benefit the public by producing better quality data and will benefit the testing facility by reducing the need to repeat nonclinical laboratory studies because of errors in the data.

131. A few comments suggested that responsibility for the standard operating procedures should be specified.

The Commissioner has concluded that this function should reside with the management of a facility, and the first sentence of § 58.81(a) is revised accordingly.

132. Several comments suggested that the responsibility for authorizing significant changes in established procedures be vested in someone other than management.

The Commissioner disagrees. Because standard operating procedure will often apply to more than one study in a testing facility, the Commissioner believes that significant changes to a standard operating procedure, which could affect several different studies, should be authorized by management.

133. Several comments stated that standard operating procedures should not apply to certain types of test systems, that the requirement would introduce difficulties in open-ended exploratory experimentation and electromedical equipment testing, that the approach would not lend itself to rapidly changing methodology such as mutagenicity testing, and that requiring chemical standard operating procedures for each test and procedure was not realistic.

The Commissioner agrees that routine standard operating procedures should not apply to exploratory studies involving basic research. He does not agree, however, that electromedical equipment testing should be exempt unless such testing does not fall under the definition of "nonclinical laboratory study." Standard operating procedures are feasible for studies using methods which change rapidly and for studies using any test system. In the case of chemical procedures, the Commissioner finds that it is realistic to require written standard operating procedures for each test.

134. One comment recommended that the phrase "written standard operating procedures" in § 58.81(a) be changed to "documented appropriate operating procedures." The same comment suggested that the term "ensure" in the first sentence of § 58.81(a) be changed to "maintain."

The Commissioner disagrees with both suggestions. The term "standard operating procedures" refers to routine and repetitive laboratory operations. "Appropriate operating procedures," as a phrase, implies that such procedures could be changed at will. The Commissioner also rejects the suggestion that "ensure" be changed to "maintain." The purpose of written standard operating procedures is to ensure the quality and integrity of the data generated in the course of nonclinical laboratory study. The term "maintain" assumes the procedures already in existence are sufficient to ensure the quality and integrity of the data when, in fact, they may not be sufficient.

135. One comment said that the term "adequate" in the first sentence of § 58.81(a) is a nonprecise term.

The Commissioner agrees, but finds that a testing facility may have a broad range of divergent standard operating procedures for many different studies and that it is impractical to define the adequacy of such procedures for all types of tests. A determination of the adequacy of each standard operating procedure is the responsibility of the management of the testing facility.

136. Numerous comments asked what changes or deviations from standard operating procedures should be documented in the raw data, as required in § 58.81(a). One comment said any deviation should be documented, whether authorized or not.

Every deviation or change in a standard operating procedure should be documented in the raw data. The second sentence of § 58.81(a) has been revised for clarity. It now reads: "All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data."

137. Seven comments indicated that it is inappropriate to require that every minor deviation be documented and reported in writing to the QAU.

The Commissioner agrees that, because the QAU is no longer required to maintain copies of standard operating procedures, it is inappropriate to require that every deviation be reported in writing to the QAU. It is sufficient that all deviations from standard operating procedures be authorized by the study director and documented in the raw data. No exceptions can be made for "minor" deviations. Because any deviation or change may affect the outcome of a study, it is not possible to judge in advance whether or not a deviation is, in fact, "minor."

138. Several comments indicated that the requirement for standard operating procedures should be general in nature.

The Commissioner disagrees. In the proposal, the Commissioner cited evidence from agency investigations of certain testing facilities that had failed to maintain written standard operating procedures of the kind outlined in § 58.81(b). As a result, certain technical personnel were unaware of the proper procedures required, e.g., for care and housing of animals, administration of test and control articles, laboratory tests, necropsy and histopathology, and handling of data. The Commissioner has concluded that a specific delineation of standard operating procedures will allow for uniform performance of testing procedures by personnel and consequent improvement in the quality of the data.

139. Two comments indicated that the requirements for standard operating procedures set out in § 58.81(b) (1) through (12) largely concern animal studies and that this should be so indicated in this section.

The Commissioner agrees that many of the provisions listed in § 58.81(b) are applicable only to studies involving animals. Such is true, however, of many provisions throughout the regulations, and no special mention of the fact is required here. The Commissioner emphasizes that operations requiring standard operating procedures are not limited to those listed in § 58.81(b).

140. One comment suggested that the phrase "and control" be deleted from the first sentence of § 58.81(b)(3), which requires standard operating procedures for test and control articles, because a control article may often be a competitor's product.

The Commissioner does not agree. Where a control article is a commercially available product, its specifications and characterization may be documented by its labeling.

141. Several comments suggested that the last sentence of proposed § 58.81(b)(3), which reads: "The testing program shall be designed to establish the identity, strength, and purity of

the test and control substances, to assess stability characteristics, where possible, and to establish storage conditions and expiration dates, where appropriate" be deleted or suggested that the sentence be transferred to another section.

The Commissioner agrees. The sentence is deleted from § 58.81(b)(3), and appropriate portions of the sentence are transferred to § 58.105(a). The concepts expressed in this sentence properly belong in the section of the regulations relating to "Test and Control Article Characterization." The phrase "testing and administration" has been deleted from the first sentence of § 58.81(b)(3) for the same reason. To specify clearly the Commissioner's intent, "method of" has been added to § 58.81(b)(3) to modify "sampling." Revised § 58.81(b)(3) now reads: "Receipt, identification, storage, handling, mixing and method of sampling of the test and control articles."

142. One comment stated that § 58.81(b)(9), "Histopathology," and § 58.81(b)(8), "Preparation of specimens," were duplicative.

The Commissioner has revised § 58.81(b)(8) to read: "Collection and identification of specimens" to distinguish the requirement from § 58.81(b)(9), "Histopathology." The term "histopathology" covers the examination of specimens, not their collection and identification.

143. Eight comments recommended a rewording of the requirement in proposed § 3e.81(b)(12) that standard operating procedures be established for the preparation and validation of the final study report.

The Commissioner concludes that the requirement should be deleted because the reporting provisions of § 58.185 adequately describe the requirements for final reports. A new paragraph, § 58.81(b)(11), covering "maintenance and calibration of equipment," has been added to reflect the requirements of § 58.63(b).

144. Seven comments suggested that in § 58.81(c) the requirement that standard operating procedures be available at all times to personnel in the immediate bench area be broadened to be within "easy access." Another comment said the location of such materials should be left to the facility's discretion.

The Commissioner has concluded that unless standard operating procedures are immediately available within the laboratory area they are not within "easy access" and may not be consulted by personnel when routine operations are being performed. The first sentence in § 58.81(c) has been edited for clarity, but the requirement remains.

145. Several comments were received regarding § 58.81(c) and the use of textbooks as standard operating procedures. One comment suggested that textbooks be considered appropriate as part of a standard operating procedure. Two comments assumed that standard operating procedures would permit the incorporation of textbooks by reference. One comment suggested that supplementary material should be written to augment textbooks. An additional comment suggested that textbooks be used in the absence of standard operation procedures.

Standard operating procedures should be set forth in writing, and textbooks may be used as supplements to written standard operating procedures. Reference to applicable procedures in scientific or manufacturer's literature may be used as a supplement to written standard operating procedures. For example, a standard operating procedure could refer to the pertinent pages of any portion(s) of a textbook or other published literature that might be pertinent to a laboratory procedure performed; these supplementary materials need not be incorporated verbatim in the standard operating procedure, but would be required to be immediately available in the laboratory area for the use of personnel. The last sentence of § 58.81(c) is revised to make this point clear. Additionally, § 58.81(d) regarding a historical file of standard operating procedures has been clarified to read: "A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained."

REAGENTS AND SOLUTIONS

146. Numerous comments on § 58.83 said that to require that the labeling of reagents and solutions in laboratory areas include the method of preparation was neither feasible nor necessary.

The Commissioner agrees and is deleting the phrase "method of preparation" from § 58.83 because the method of preparation could be too lengthy to fit readily on the label. The method of preparation of reagents and solutions should, however, be addressed by the standard operating procedures.

147. Several comments stated that the provision for the handling and use of deteriorated materials and materials of substandard quality should specify only that they not be used and should not specify or require their removal from the laboratory because their removal should be left to the discretion of the laboratory.

The Commissioner agrees, and § 58.83 has been revised accordingly.

148. One comment suggested that the phrase "used in nonclinical studies" be substituted for the phrase "in the laboratory areas" in the first sentence of § 58.83.

The Commissioner disagrees with this comment. All reagents and solutions used in a laboratory conducting a nonclinical study should be properly labeled as provided in the regulation to preclude inadvertent mixups of reagents and solutions that are used in such studies with those that are not intended for such use.

149. Two comments suggested that the phrase "Deteriorated materials and materials of substandard quality" in the second sentence of the section be changed to incorporate the terms "reagents" and "solutions."

The Commissioner agrees and is revising the second sentence of § 58.83 accordingly. Revised § 58.83 now reads: "All reagents and solutions in laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used."

ANIMAL CARE

150. Several comments raised the issues of unnecessary animal experimentation and the humane care of animals.

The issue of using animals in laboratory experiments designed to establish the safety of regulated products has been raised many times in the course of agency rulemaking. The position of FDA has been consistent on this issue. The use of animal tests to establish the safety of FDA-regulated products is necessary to minimize the risks from use of such products by humans. The humane care of test animals is a recognized and accepted scientific and ethical responsibility and is encouraged both by various agency guidelines and the Animal Welfare Act. The good laboratory practice regulations should, in fact, encourage the humane treatment of animals used in nonclinical laboratory studies by establishing minimum requirements for the husbandry of animals during the conduct of such studies. In addition, there should occur a reduction in the amount of animal testing that has to be repeated or supplemented because the original studies were inadequate or inappropriate to establish the safety of FDA-regulated products.

151. Numerous comments objected to the incorporation by reference of guidelines and standards proposed in § 58.90(a).

As noted early in the preamble, all references to other standards such as the Animal Welfare Act of 1970 and HEW Publication No. (NIH) 74-23 have been deleted. Section 58.90(a) is revised to read: "There shall be standard operating procedures for the housing, feeding, handling and care of animals."

152. Several comments stated that the quarantine of animals required in

§ 58.90(b) was impossible in some cases, unnecessary under certain conditions, and would prevent the use of certain animals, such as "timed-pregnant" mice. Other comments said the paragraph could be interpreted to require a separate quarantine area or an extensive quarantine time period.

The purpose of this paragraph is to require that the health status of newly received animals be known before they are used. This requires a separate quarantine area where necessary to determine animal health status. The concept of "separate areas" has been previously discussed. In some cases, depending on such factors as the species or type (e.g., time-pregnant) of animal, or the source and the nature of the expected use of the animal, a health evaluation can be made immediately, or soon after arrival, resulting in a very short quarantine period. The regulation does not preclude this type of health evaluation if it is done in accordance with acceptable veterinary medical practice.

153. Several comments stated that quarantine is unnecessary when animals are obtained from reputable or specific pathogen-free sources.

A health evaluation is required of all newly received animals regardless of the supply source, although the source can be a factor in determining the degree or depth of health evaluation required. Seldom can the conditions under which animals are transported from their source be considered certain to preclude the possibility of exposure of the animals to disease.

154. Some comments requested deletion of § 58.90(b) because it duplicates the animal care requirements regulations.

The Commissioner rejects these comments. The agency is responsible for animal care procedures as they pertain to testing facilities conducting nonclinical laboratory studies, and the provisions are appropriately included in § 58.90(b).

155. Several comments said that the requirements of § 58.90(c) and (d) concerning the isolation of known or suspected diseased animals and keeping animals free of disease or conditions that would interfere with the conduct of the study were impractical.

For clarity, these paragraphs are revised and combined in § 58.90(c). This paragraph deals only with those diseases and conditions that might interfere with the study. This excludes a wide range of diseases and conditions and allows the consideration of such factors as etiology and whether the disease is communicable. The section does not require isolation of all animals in a shipment from a study when only one or some of the animals are diseased, and it covers only those animals that are known or suspected to be diseased.

156. Some comments suggested that specific requirements be provided for the management of diseased animals, and one comment said the veterinary staff should be able to treat diseased animals as they deem proper.

The Commissioner concludes that it is beyond the scope and purpose of these regulations to describe detailed requirements concerning the management of diseased animals and that § 58.90(c) is sufficiently explicit to exclude the use of diseased animals that would interfere with the purpose or conduct of a nonclinical laboratory study. The regulation does not prohibit the treatment of diseased animals if such treatment does not interfere with the study. If treatment will interfere with the study, the diseased animals shall be removed from the study.

157. More than 60 comments objected to or requested revision of proposed § 3e.90(e), which called for the unique identification of all animals used in nonclinical laboratory studies. Fifty-four of the comments addressed specific issues related to this concept, e.g., unique identification of mice, costs of such systems, application to suckling rodents, injury to animals from identification systems, effects of dyes or tattoos, a lack of need in single-dose or short-term experiments, and cage identification instead of animal identification with precautions being taken to prevent animal mixups.

In the absence of a proven and acceptable method of unique identification for small rodents, the Commissioner is revising § 58.90(d) to require appropriate identification for warm-blooded animals, excluding suckling rodents, which require manipulations and observations over extended periods of time. Suckling rodents have been excluded from the requirements because of potential cannibalization by the mother. The same information needed to specifically identify each animal is required on the outside of housing containers or cages. Such identification should substantially reduce the possibility for animal mixup. Because of the varied nature of the tests conducted and the test systems used, the manner of identification is left to the discretion of the testing facility.

The Commissioner advises that whenever a study requires that animals be removed from and returned to their home cages, there is a potential for mixup. Thus, if a single-dose or short-term study requires such manipulations, the animals shall receive appropriate identification.

Because the requirement for unique identification has been deleted, the concerns expressed regarding cost, injury to the animals from various identification systems, and the effects of dyes or tattoos are no longer germane.

158. Two comments questioned whether the study director could in practice assure unique identification as proposed in § 3e.90(e), without direct observation.

The requirement has been deleted, along with the requirement for unique identification.

159. Two comments requested deletion of the last sentence of proposed § 3e.90(e) regarding the identification of specimens.

The Commissioner concludes that proper specimen identification is an integral part of proper study conduct, but that the requirement more properly belongs under standard operating procedures. Consequently, § 58.81(b)(8) now incorporates this provision.

160. One comment inquired whether, in the event animals of the same species in different tests were in the same room, FDA would require identification of all compounds. This, it was felt, would raise confidentiality questions for a contract testing facility.

The Commissioner advises that the use of coding to identify test or control articles is not precluded by § 58.90(e). The concluding phrase, "to avoid any intermixing of test animals," was deleted as redundant.

161. Proposed § 3e.90(g) required comparison of cage and animal identification for each transfer, procedures for verification, and written permission of the study director for location transfer. Seventeen comments objected to part or all of these requirements as vague, burdensome, unnecessary, and redundant.

The Commissioner agrees, and the paragraph is deleted. Procedures for the transfer and proper placement of animals are required as standard operating procedures in § 58.81(b)(12).

162. Several comments claimed that the requirements of proposed § 3e.90(h), redesignated § 58.90(f), were redundant in view of the requirement for standard operating procedures in § 58.81. Other comments stated that the incorporation of guidelines by reference was inappropriate.

The Commissioner concludes that the requirement that animal cages, racks, and accessory equipment be cleaned is appropriately included in this section even though there is some overlap with the language of § 58.81, standard operating procedures. The reference to other agency guidelines has been deleted.

163. Three comments asserted that sanitization should not always be done, because it could in certain cases interfere with the conduct of the study.

The Commissioner agrees and points out that the language in redesignated

§ 58.90(f) permits cleaning and sanitization at appropriate intervals. The section now reads: "Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals."

164. Many comments objected to proposed § 3e.90(i), redesignated § 58.90(g), which requires periodic analysis of feed and drinking water for "known interfering contaminants." Certain of these comments requested clarification or deletion, or expressed concern about the costs involved. Others argued that the use of positive and negative controls would accomplish the intent of the requirement, or that certificates of analysis from local water supply authorities and feed manufacturers should be permissible. Finally, a few comments said analysis of feed and water should only be required when there is reason to believe that a particular contaminant may have an effect on the study, and comments said the analysis requirements should be specified in the protocol.

Most of the objections raised against the analytical requirements of the section were based on misinterpretation of such requirements. The intent of the Commissioner was to require analysis for contaminants known to be capable of interfering with the nonclinical laboratory study and reasonably expected to be present in the feed or water, and not to require analysis of feed and water for all contaminants known to exist. Certain contaminants could affect study outcome by masking the effects of the test article, as was observed in recent toxicological studies of pentachlorophenol and diethylstilbestrol, in which the feeds used as carriers for the test articles were found to contain varying quantities of pentachlorophenol and estrogenic activity, respectively, that invalidated these studies by producing erratic results. The use of positive and negative controls in these examples was insufficient to compensate for the variability in contaminant content. Therefore, the Commissioner agrees with the comments that suggested that analysis of feed and water only be done when there is reason to believe that a particular contaminant may have an effect on the study, and may be present in the feed or water, and the language of both redesignated § 58.90(g) and § 58.120(a)(9) have been revised to make this clear. This clarification of the regulations should allay the concerns of those comments relating to certificates of analysis, costs, and precise definition of impurities. Acceptable contaminant limits must be specified by the protocol (§ 58.120(a)(9)), and should be determined at the time the protocol is developed, taking into account the scientific literature, the availability of suitable analytical methodology, and the practicability of controlling the level of the contaminant.

165. One comment suggested additional requirements for, e.g., analysis of nutrients and reserve samples of feed at the testing facility.

Nutrient analysis should be addressed by the facility's standard operating procedures. Requirements for reserve samples of test or control articles/carrier mixture (e.g., feed) are set forth in § 58.113(b). The Commissioner concludes that minimum requirements for those items are set forth in the regulation. The regulation does not preclude the setting of additional requirements by the sponsor and/or the testing facility.

166. Proposed § 3e.90(j) would have required feed to bear an expiration date. Twenty-three comments argued that this requirement is of dubious value, is beyond the current state of the art because of varied storage conditions, and that commercially available feed is not expiration dated, making the requirement impractical or impossible.

The Commissioner agrees with these comments, and this requirement is deleted.

167. Several comments argued that the requirement for weekly changes of bedding should be deleted. The comments stated that, in certain cases, weekly bedding changes are contraindicated.

The Commissioner agrees, and the phrase "at least once per week" is removed from § 58.90(h), which now reads, "Bedding * * * shall be changed as often as necessary to keep the animals dry and clean."

Test and Control Articles

Test and control article characterization

168. One comment suggested that § 58.105 be deleted; another suggested that the entire subpart be condensed; and three comments suggested that the section is not generally applicable to nonclinical device studies, particularly with reference to such terms as "identity, strength, quality, and purity."

The Commissioner does not agree that the section should be deleted. Its purpose is to assure that the article being tested has been thoroughly characterized or defined and that either the sponsor or the testing facility has a thorough understanding of what is being tested. The Commissioner agrees that the subpart should be condensed and has shortened it. Section 58.105(a) is modified by the inclusion of the sentence "the identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article." This addition provides for characterization of various products, including devices in terms suited to their identity or uniqueness.

169. One comment argued that the requirement that "other substances contained in the test and control substances" be accounted for, as proposed in § 58.105(a), was vague.

By this provision the Commissioner intended to indicate the need to identify and characterize solvents, excipients, inert ingredients and/or impurities that might be part of the test substance. Because these materials are included by definition in the term "test article," the Commissioner has determined that the original language was unnecessary and has deleted it.

170. Three comments sought definition of the word "batch" as used in § 58.105(a).

The term "batch" is now defined in § 58.3(n).

171. Seventeen comments on § 58.105(a) stated that because some control or reference articles might be a competitor's or a supplier's product, the assay and method of synthesis might not be available or might be confidential.

The Commissioner concludes that, in those cases where a competitor's or supplier's product is used as a control article, such products will be characterized by the labeling and no further characterization is necessary.

172. One comment stated that the testing facility should not be responsible for identity, strength, quality and purity and that this responsibility should rest with the sponsor. This comment also suggested that the requirement, as written, would inhibit the conduct of blind studies.

The Commissioner concludes that it is the responsibility of testing facility management to assure that the requisite tests have been done, either by the sponsor or by the test facility (see § 58.31(d)). In those cases where a testing facility is unable to perform the characterization test or is performing blind studies, the sponsor should perform the required testing and notify testing facility management that the characterization of the test or control article has been performed. The section, as revised, does not inhibit the conduct of blind studies: it does not require that the sponsor give the characterizing information to the testing facility, only that the sponsor notify the testing facility that the required characterization has been done.

173. One comment suggested that the requirements of § 58.105 should only apply if the integrity of the study is threatened, and another suggested that any contaminants in a test or control article should be evaluated only with respect to their impact on study validity.

The Commissioner does not agree that the requirement should be so limited. Thorough characterization of the article under test is essential because the results of the test may be compromised by possible contamination. Only by knowing the identity and quantity of the components can one predict their effect on the study. The evaluation of the impact of test and control article contaminants on the validity of the study is an important part of the thorough characterization of the test and control articles.

174. Thirteen comments suggested that characterization of the test article be permitted during the study, after its completion, or left to such time as specified in the protocol.

The Commissioner concludes that characterization of the test or control article should be determined before the initiation of the study in order to provide a means of controlling variations from batch to batch as well as to make certain that the test article meets the specifications of the protocol. As previously stated, a thorough understanding of the nature of the test article is a basic requirement for assuring the absence of contaminants that may interfere with the outcome of the study. When the stability of the test and control articles has not been determined before initiation of the study, the regulation requires periodic reanalysis of each batch of test and control articles as often as necessary while the study is in progress.

175. One comment stated that the phrase "verifying documentation" in § 58.105(a) was not clear.

The Commissioner has determined that the phrase is not needed, and § 58.105(a) is revised to delete it.

176. Seven comments suggested that stability studies required by § 58.105(b) may not always be necessary; three comments suggested that common vehicles and placebo controls, such as water, should be omitted from stability studies.

Some degree of instability may be associated with every test article that might be the subject of nonclinical laboratory study. The Commissioner concludes, therefore, that stability information must be included as part of the information upon which the agency bases a decision regarding the safety of the article. If the stability of common vehicles is generally recognized and can be documented, stability testing is not required.

177. Twelve comments suggested that the term "production" in proposed § 3e.105(c) should be deleted or changed by substitution of other terms such as "approved" or "released," stating that the use of the word was confusing. Several other comments stated that the requirement that test and control substances be derived from the smallest number of production batches consistent with their stability was not always possible or necessary.

The Commissioner agrees that the section was confusing and finds that the requirement is adequately covered by § 58.105(a). The word "batch" has been defined in § 58.3(n), and proposed § 3e.105(c) has been deleted.

178. One comment suggested that the test and control articles should be derived from a large number of batches to increase the probability that test and control articles are representative.

The Commissioner agrees that, in some cases, combining representative samples of test or control articles from various production sources or lots to form a batch may be desirable. Where this is done, however, the resulting batch, rather than the individual samples, must be characterized in accordance with § 58.105(a).

179. Eight comments on § 58.105(d) suggested that the requirement for reserve sample retention be restricted to those substances whose stability had not been previously determined. Another comment suggested that the section seems to require that a reserve sample of water be retained if water is used as the control article, and another comment suggested that the retention of a reserve sample should be left to the discretion of the sponsor.

The Commissioner does not agree that the decision to retain a reserve sample should be at the discretion of the sponsor. Maintaining a reserve sample is necessary to provide independent assurance that the test system was exposed to the test article as specified in the protocol. Reserve samples need not be reanalyzed routinely if the stability of the test or control article is well established. If, however, the results of a study raise questions as to the composition of the test or control article, retention of reserve samples allows resolution of the question. Retention of a reserve sample of water is required when it serves as the control article in a nonclinical laboratory study.

180. Eight comments on § 58.105(d) suggested that containers should be comparable rather than identical to maintain approximate ratio of mass of article to container volume.

Reserve samples should be stored in containers and under conditions that maximize their useful life. The specifications for containers are deleted from § 58.105(d), however, and are now left to the discretion of the study director.

181. Six comments said § 58.105(d) duplicated §§ 58.105(b) and 58.113(a)(2); three said that the requirement that the reserve sample be analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date may result in unnecessary testing. One comment suggested that a portion of the remaining article should be tested rather than testing the reserve sample.

The Commissioner agrees that the requirement for routine reanalysis of all test or control articles is unnecessary where stability characteristics have been well established, and this requirement has been deleted. The Commissioner does not agree that the cited sections duplicate one another. Section § 58.105(b) concerns the stability of test and control articles in a carrier mixture. But § 58.105(d) concerns reserve samples of test and control articles.

182. A number of comments on proposed § 3e.105(f) sought clarification of the requirements, definition of the term "quarantine," and deletion of the requirement to reanalyze batches returned from distribution.

The Commissioner has examined the provision as proposed and has found that the intent is achieved by the provisions of § 58.107 (test and control article handling). Proposed § 3e.105(f) has, therefore, been deleted.

TEST AND CONTROL ARTICLE HANDLING

183. One comment asserted that § 58.105 covered the specifics for handling test and control substances and that § 58.107 should be deleted.

The Commissioner disagrees with the assertion that § 58.107 repeats § 58.105. The provisions of § 58.105 apply to the characterization of test and control articles and their storage prior to use. Section 58.107 sets forth provisions for the handling and distribution of test and control articles during the course of a nonclinical laboratory study. The purpose of this section is to provide further mechanisms to assure that test and control articles meet protocol specifications throughout the course of the study, and that test article accountability is maintained.

184. Other comments argued that the language of § 58.107 should be modified and that, as written, the section was impractical.

The Commissioner does not agree that the requirements are impractical. The section has, however, been edited for clarity. Section 58.107(a) now reads, "There is proper storage." Because contamination is only one of the consequences that may result from improper handling during distribution, the Commissioner has revised § 58.107(b) to read: "Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage."

MIXTURES OF ARTICLES WITH CARRIERS

185. Many comments stated that the requirements of § 58.113 should only apply to certain types of studies, such as long term feeding studies, or should apply only in cases where problems of instability might result from mixing the test article with a carrier.

The Commissioner does not agree. The need to know that the test system is being exposed to the amounts and types of test and control articles that are specified in the protocol is common to all types of studies. The effect of mixing on the concentration and stability of the test or control article in the mixture cannot be predicted beforehand.

186. Six comments stated that the requirement that each batch of a test or control article that is mixed with a carrier be tested for uniformity of mix, stability, and release, as proposed in § 58.113, was excessive.

The Commissioner has reviewed the reasons advanced by the comments and has deleted the "for each batch" requirement. Once the uniformity of the mixture has been established for a given set of mixing conditions, it is not necessary to establish the uniformity of each subsequent batch that is mixed according to the same specifications. Similar considerations apply to stability testing. Section 58.113(a)(1) introductory text and (a) now read: "For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted: (1) to determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture." The sentence, "[I]f the nonclinical study is to be performed as a blind study, enough individual samples of the mixture shall be returned to the sponsor for analysis," has been deleted. The requirement for analysis of test or control article mixtures is adequately addressed by the revised language of § 58.113(a)(1). The mechanism of satisfying the requirement is left to the testing facility. Blind studies are discussed in paragraph 172 above.

187. One comment stated that the possibility of administration by other than the oral route should be considered.

The Commissioner agrees, and reference to the route of administration is removed.

188. Several comments said the acute and subacute toxicity studies are often conducted before there is extensive knowlege about a drug's stability and that in such cases the drug might be prepared daily. In addition, it was suggested that § 58.113(a)(2) allow for concurrent stability studies.

The Commissioner agrees with the comment and has revised the regulation to allow concurrent studies of stability to proceed with the ongoing nonclinical laboratory study.

189. Three comments on § 58.113 suggested that establishing expiration dates for a substance used up in a week seemed too stringent. Many comments suggested that the expiration dating requirement be eliminated entirely because batch sizes are established so that they will be used up prior to deterioration of the test article.

The Commissioner has considered the comments and has revised, as noted above, the requirement for labeling each batch of test or control article carrier mixture to permit concurrent stability testing. The Commissioner declines to eliminate entirely the requirement for listing of expiration dates. Expiration dates should be used, when known, to minimize the possibility that subpotent, unstable, or decomposed test or control article carrier mixtures will be used. New § 58.113(c) requires that, where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

190. Many comments on proposed § 3e.113(a)(3) stated that the requirement for tests to determine the release of the test or control substance from the carrier needed to be clarified, might be impossible to do, and were not always necessary.

The Commissioner has reviewed the comments and the section and finds that such testing should be adequately addressed by the protocol. He has, therefore, deleted the section.

191. Eleven comments suggested that the requirement that reserve samples of each batch of test or control article-carrier mixture be retained was excessive and impractical.

The Commissioner does not agree. Maintenance of reserve samples of these mixtures is necessary for the same reasons that reserve samples of test and control articles themselves are necessary. These reasons are stated in paragraph 179 above.

192. Proposed § 3e.115 incorporated principles set forth in other regulations and has, accordingly, been deleted. (See the discussion in paragraph 3.)

PROTOCOL FOR AND CONDUCT OF A NONCLINICAL LABORATORY STUDY

PROTOCOL

193. Several comments said the protocol requirements of § 58.102(a) were not relevant to specific test articles, e.g., electronic diagnostic instrumentation. Other comments objected to requiring a protocol for short-term studies or for routine tests described elsewhere in 21 CFR Chapter I. Additional comments proposed that specific requirements be imposed only where applicable, and one comment said the protocol should focus on what is intended rather than on how the intended result is to be achieved.

The Commissioner has previously discussed the types of tests and the conditions within the scope of Part 58. Because of the broad range of studies covered, specific sections may not apply to all studies. However, the Commissioner declines to exempt short-term studies or routine tests from these requirements. Any study which qualifies as a nonclinical laboratory study is subject to the requirements. The good laboratory practice regulations are both process-oriented and product-oriented, and are designed to ensure, insofar as possible, the quality and integrity of nonclinical laboratory data submitted to FDA in support of regulated products. The Commissioner recognizes that some of the requirements of this section have often not been traditionally included in a protocol. He has nonetheless concluded that the requirements are essential to ensure that all operations needed to fulfill the objectives of a study are performed and that the complete list of information required by this section is necessary to ensure that deviations, should they occur, are readily appparent.

194. One comment asked what was meant by "all methods" in § 58.120; one suggested deletion of the word "approved" to describe the protocol; and another suggested that reference to statistical methods in § 58.120(a) be deleted and that a new paragraph on statistical methods be added to the list of information required.

"All methods" refers to all operations necessary to achieve the objectives of the study, e.g., analytical methods, randomization procedures, etc. If such methods are from published sources, citation of the source would fulfill this requirement. If the methods are not from published sources, full descriptions would need to be included in the protocol. The word "approved" is retained to emphasize that a sponsor or testing facility should have a mechanism for evaluation and approval of initial protocols and all amendments. A new paragraph (a)(16) is provided to emphasize the need to consider statistical methodology in preparing a protocol.

195. Ten comments objected to the inclusion, in proposed § 3e.120(a)(3), of stability methodology as a protocol requirement because such methodology may not have been developed before the study was begun. Another comment suggested deletion of this requirement as not relevant to a proto-

col, while three comments suggested revision.

The Commissioner recognizes that stability data may not be available when a study is initiated, and this requirement is deleted from the section. The Commissioner emphasizes, however, that determination of the stability of the test and control articles is a responsibility of the study director, that determination of the stability of the articles per se is required under § 58.105(b), and that determination of the stability of the article/carrier mixes is required under § 58.113.

196. Numerous comments on proposed § 3e.120(a)(4) objected to the listing of the names of laboratory assistants and animal care personnel in the protocol because these jobs are subject to constant turnover or periodic rotation.

The Commissioner agrees that laboratory assistants and animal care personnel need not be identified in the protocol. The list of personnel required to be named is transferred to § 58.185(a)(12).

197. One comment proposed that listing the name of the sponsor and name and address of the testing facility required by § 58.120(a)(3) be restricted to studies done under contract.

The Commissioner does not agree with restricting this requirement to studies done under contract because a testing facility, though a division of the sponsor, may have a specific designation and a location different from the sponsor's, and this information is necessary to determine the exact location of the study.

198. Numerous comments on § 58.120(a)(4) objected to specifying starting and completion dates in the protocol because changing priorities may make such specification impractical. Another comment proposed deletion of the requirement for dates as not relevant to a protocol.

Changing priorities may cause changes in starting dates. For this reason the requirement calls for the proposed dates. If the actual dates differ from the proposed dates, the change should be reflected in a protocol amendment. The dates may be needed in the reconstruction of the study.

199. Ten comments on proposed § 3e.120(a)(7) objected that the proposed date for submission of the final study report to management or to the sponsor was not relevant to a protocol, and one requested a definition of the term "completion date."

The Commissioner agrees that the proposed submission date is not relevant, and the provision is deleted.

200. Numerous comments on § 58.120(a)(6) suggested requiring age of the test system only where applicable or substituting age range for age. Several objected to the requirement for justification for selection of the test system as not relevant to protocol requirements. Additional comments proposed that the requirement for justification be limited to nonroutine systems.

The Commission agrees that age of the test system may not always be critical, and § 58.120(a)(6) now requires number, body weight range, sex, source of supply, species, strain and substrain, and age of the test system only "where applicable." The Commissioner does not agree that justification for selection of the test system is not relevant to a protocol or should be limited to nonroutine systems. Such justification is an integral and essential part of every protocol and to emphasize its importance, the Commissioner is establishing a separate paragraph for this requirement, § 58.120(a)(5).

201. Several comments on § 58.120(a)(8) (proposed § 3e.120(a)(10)) objected that the method of randomization was not relevant to the protocol and suggested requiring justification for the selected method only when nonroutine methods are selected; four comments said justification of the method of randomization is unnecessary; and one comment proposed revised language regarding method of randomization.

The Commissioner finds that the method of randomization or other methods of controlling bias are relevant and are essential parts of a protocol, whether the methods used may be described as routine or nonroutine. The suggested revision is adopted in part, and § 58.120(a)(8) now reads: "A description of the experimental design, including the methods for the control of bias."

202. One comment said a description of the diet used in the study (proposed § 3e.120(a)(11), now § 58.120(a)(9)) was unnecessary unless the diet was unusual. The comment further said that the necessity for including solvents and emulsifiers was questionable because these might not be known at the time the protocol is written.

The Commissioner advises that the phrase "and/or identification" in § 58.120(a)(9) permits a commercial animal diet to be identified by its name. The need for using solvents or emulsifiers may not be known when the protocol is written; however, when this information is available and the solvents, etc., are selected, this fact should be reflected in a protocol amendment.

203. Nine comments pointed out that the degree of absorption (proposed § 3e.120(a)(14)), now § 58.120(a)(12)) is usually unknown at the time of the preparation of the protocol.

The Commissioner recognizes that absorption studies may be conducted concurrently with or as part of the nonclinical laboratory study and points out that the requirements of § 58.120(a)(12) can be fulfilled by amending the protocol.

204. Nine comments suggested deletion of the requirement that the protocol include the records to be maintained (proposed § 3e.120(a)(16), now § 58.120(a)(14)) because this duplicates the requirements under another provision of the regulation.

The Commissioner concludes that the protocol should include a plan identifying the records to be maintained and, therefore, does not agree that § 58.120(a)(14) should be deleted.

CONDUCT OF A NONCLINICAL LABORATORY STUDY

205. Several comments objected to the § 58.130(c) requirement that specimens be identified. Three comments proposed revisions to eliminate the list of specific items (test system, study, nature, date of collection) included for identification of specimens. Numerous comments objected to the identification system as overly restrictive, stating that a coding system should be permitted.

The Commissioner rejects the suggested modifications because the requirements are designed to preclude error. The specific items required to identify a specimen are the minimum necessary to prevent mixup of specimens and permit orderly storage. The Commissioner does not agree that this system is overly restrictive because it does not preclude a coding system.

206. Numerous comments objected to the requirement, in § 58.130(e), for recording data in bound books with prenumbered pages as costly, time-consuming, overly restrictive, and difficult for long-term studies. Six were concerned that much information is too voluminous to be recorded directly and that reference to other documents should be permitted to justify changes, and two comments objected to recording "dictated observations" in ink.

The Commissioner agrees that the requirement for bound books is too restrictive in view of both the variety of data recording procedures that can be used in nonclinical laboratory studies covered by this part and the many ways in which data are generated and collected for these studies. He is, therefore, revising the section. As revised, § 58.130(e) does not preclude reference to other documents if the documents are clearly identified and available. The requirements of the section can be met by maintaining the dictation media or an exact transcription.

207. Three comments proposed that § 58.103(e) be revised to reflect the

three types of computer entries, i.e., direct on-line recording, input from computer readable forms, and input transcribed from recorded raw data. An additional comment suggested revised language to achieve this purpose; and two comments stated that computer printouts of interim display data need not be maintained when the data are wholly contained in subsequent iterations.

The revised wording of § 58.130(e) is equally applicable to the various forms of computer data entries. The Commissioner advises that where the data for computer input are in machine-readable form, such as marketed-sense cards, or are transcribed from recorded raw data, the machine-readable forms or the recorded raw data would constitute raw data within the definition of this part. Where input is via direct on-line recording, the magnetic media and the program would constitute raw data within the meaning of this part.

208. Three comments objected that a daily signature and date for each entry would be burdensome in studies involving daily measurements on each animal.

Section 58.130(e) does not require signing and dating of every individual item recorded. An entry can consist of several observations of several animals made by the same person.

209. Three comments suggested deletion of proposed § 3e.130(f), which required the review of all recorded data, because this duplicated the function of the study director.

The Commissioner agrees that these requirements are adequately addressed by § 58.33(b), and the paragraph is deleted.

RECORDS AND REPORTS

REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

210. Seven comments said the requirement that the final report include all raw data and calculations proposed in § 3e.185(a)(3) is not practical and that a recapitulation should be adequate.

The Commissioner agrees, and the requirement that all raw data be included in the final report is deleted.

211. Two comments on § 58.185(a)(3) stated that the scope of the term "method" was not clear.

The Commissioner advises that "method" does not mean that either the actual calculations or a step-by-step reiteration of the process be included. The name of the method, the description of the method, or a reference to an article or test describing the method will be sufficient.

212. Several comments on § 58.185(a)(4) stated that the final report should provide only a reference to the information on "strength, quality, and purity" rather than the actual values for those characteristics.

The Commissioner does not agree. The final report should include actual values for all characteristics required for proper identification. Because the actual values for strength, quality, and purity are not, in every case, sufficient for adequate identification, the word "quality" has been stricken and the words "and composition or other appropriate characteristics" have been added. The additional language will permit the use of any characteristic which facilitates identification of the test and control article.

213a. Several comments on § 58.185(a)(5) stated that the requirement that stability of the test and control articles be described should be narrowed.

The Commissioner finds that stability information must be submitted as part of the final report. The extent of stability testing required by these regulations is discussed at paragraphs 176, 185, 186, and 189 above.

b. Comments on proposed § 3e.185(a)(8) (now § 58.185(a)(7)) requested that the words "appropriate and necessary" be inserted following the words "procedure used", for identifying the test system.

The Commissioner is modifying § 58.185(a)(7) to require reporting such details where applicable.

214. Seven comments on § 58.185(a)(12) protested the requirement that the final report include reports of each of the individual scientists or other professionals involved in the study.

The Commissioner concludes that the individual reports are required to assure that the final results reported accurately reflect the findings of the individual scientists.

215. A number of comments on § 58.185(a)(3) objected to reporting the location of the raw data in the final report.

For the purpose of information retrieval, the Commissioner is of the opinion that the location of the raw data should be specified.

216. The Commissioner advises that the list of personnel required to be named in the final report as specified in § 58.185(a)(12) has been broadened to include all professionals. (See paragraph 196 above.)

STORAGE AND RETRIEVAL OF RECORDS AND DATA

217. Several comments requested revision and clarification of "other information" in § 58.190(a).

The phrase "and other information" is deleted because it is subsumed by the specific requirements for documentation.

218. Five comments requested clarification of the term "specimen" as used in § 58.190(b).

The term "specimen" is defined in § 58.3(j) and means any material derived from a test system for examination or analysis. This includes wet specimens, histological blocks, and slides that yield information pertinent to the outcome of the study. Such specimens are required to bear sufficient labeling to permit identification and expedient retrieval.

219. Several comments stated that the prohibition against "intermingling" of specimens was unnecessary if specimens are properly labeled and indexed.

The Commissioner agrees and finds that the storage requirements are adequate to achieve their purpose without any further prohibitions. The reference to intermingling of samples is, therefore, deleted.

220. Seven comments said proposed § 3e.190(c) was unclear or redundant and required the maintenance of unnecessary duplicative files by both the testing facility and the sponsor.

The Commissioner agrees with the comments, and the paragraph is deleted.

221. A number of comments requested that § 58.190(c) provide that more than one person be permitted to be responsible for the archives.

The Commissioner reaffirms the need for one individual to be accountable for the maintenance and security of the archives to prevent access by unauthorized personnel. Such access could lead to the loss of, or damage to, records and specimens required to be maintained by these regulations. This provision does not preclude delegation of duties to other individuals who may help maintain the archives.

222. Comments on § 58.190(e) suggested that coding of archival contents should be allowed and objected that the section would require four-way indexing.

The paragraph is revised for clarity. As revised, the use of a coding system is permitted; however, the cross-reference indexing system is retained as a requirement.

223. Section 58.190(g) is deleted because the inspection requirements are adequately addressed by § 58.15.

RETENTION OF RECORDS

224. Several comments stated that the proposed record retention requirements were inconsistent with those previously established.

A new paragraph (a) is added to § 58.195 to make it clear that the record retention requirements of this section do not supersede those of any other regulations in this chapter.

225. Several comments pointed out that IND's are not "approved" and

asked that the record retention requirements for IND's be clarified.

The Commissioner agrees that the record retention requirements, as they apply to both IND's and IDE's, need clarification. In addition to the fact that IND's are not, in a technical sense, "approved," the Commissioner has considered the fact that when either an IND or an IDE is submitted to the agency, the application may contain voluminous data collected over a number of years. It was not the intent of these regulations that such supporting IND or IDE data be destroyed after 2 years because not all studies submitted at the time of filing may be of interest to the agency until several years after submission. Therefore, a new sentence is added to § 58.195(b)(1), which states that the 2-year retention requirement does not apply to studies supporting notices of claimed investigational exemptions for new drugs (IND's) or applications for investigational device exemptions (IDE's). These records are governed by § 58.195(b)(2) and shall be retained for at least 5 years. This additional language clarifies both agency policy and current scientific practice which is, in most cases, to maintain such study records far longer than 5 years.

226. One comment said the variable record retention periods are unworkable, and another said records should be maintained as long as the public is exposed to a chemical.

The record retention period represents the minimum deemed appropriate. For uniformity, all records may be retained for 5 years. Longer retention periods are unnecessary because each nonclinical testing facility will be inspected every 2 years. Studies conducted at facilities that are in substantial compliance with these regulations will be presumed to be valid. When significant deviations are discovered, steps will be taken to validate individual studies before the record retention period expires.

227. Twenty-three comments on § 58.195(b)(3) objected to the record retention requirement as it applies to terminated or discontinued studies, stating that the requirement goes beyond the intent expressed in the definitions or that FDA lacks the authority to require that such studies be retained.

The Commissioner finds that such studies are frequently capable of yielding information applicable to evaluations of related compounds. In the interest of the public health, all such data derived from studies originally intended to be submitted to the agency should be available to the agency. This is particularly important when studies are terminated because of preliminary findings that the test article causes adverse effects at such low levels that any safe use of the article is precluded. The general question of FDA's authority is discussed in paragraph 5 above.

228. With respect to retention of appropriate samples, including wet specimens, several comments on § 58.195(c) requested that the regulations specifically set forth conditions of storage. Others felt that this requirement would be of doubtful value, and several were concerned that the retention period not exceed that which could adversely affect sample integrity.

The Commissioner states that it would be impractical to attempt to specify the specific storage conditions for sample retention. This should be left to the judgment of the testing facility. It is essential as a check on recorded observations that, wherever possible, samples be retained for confirmation of findings. Such samples should be retained for the minimum period specified in the regulations. The regulation clearly states that fragile samples shall be retained only so long as the quality of the preparation affords evaluation.

229. Three comments on § 58.195(e) objected to archive retention of curricula vitae and job descriptions of all personnel involved in the study.

Section 58.195(e) is revised to permit this information to be retained as part of the testing facility employment records.

230. One comment on § 58.195(f) stated that equipment records should be maintained in an independent log rather than maintained as part of each study.

The Commissioner advises that the language of the section does not preclude such an approach. Records of maintenance and calibration of equipment may be kept in a repair manual or on a tag affixed to the instrument. The reference to cleaning records is deleted.

Disqualification of Testing Facilities

PURPOSE

231. Many comments were received concerning the general concept and purpose of disqualification.

The Commissioner believes that many of these comments were based, at least in part, on misunderstanding of the frequency with which disqualification might be used. The Commissioner believes disqualification is an important alternative to rejection of specific studies and legal prosecution because it can reduce by consolidation the number of FDA investigations and administrative proceedings that might be required if FDA acted only on a study-by-study basis. To clarify the agency's intent regarding the disqualification mechanism and to allay fears that this sanction might be abused, the Commissioner is revising Subpart K of the regulations to define more clearly the grounds for disqualification.

231. Section 58.200(a) has been revised to clarify the purposes of disqualification. The first purpose stated in the section is to permit FDA to exclude from consideration any completed studies conducted by a testing facility which has failed to comply with good laboratory practice requirements until it can adequately be demonstrated that the noncompliance did not occur during, or did not affect the validity of data generated by, a particular study. Thus, for studies completed before disqualification, the order of disqualification creates a rebuttable presumption that all studies previously conducted by the facility are unacceptable. Such a study may be accepted, however, upon presentation of evidence demonstrating that the noncompliance which resulted in the disqualification did not affect the particular study. The second purpose set forth in the revision of § 58.200(a) is to exclude studies completed after the date of disqualification from consideration until the facility can satisfy the Commissioner that it will conduct studies in compliance with the regulations. (See also the discussion in paragraph 241.)

GROUNDS FOR DISQUALIFICATION

232. Many comments argued that the disqualification provisions appeared to be overly harsh, arbitrary, and ambiguous.

To clarify the agency's intent, the Commissioner is revising the section. The primary function of the agency's regulation of nonclinical laboratory testing is to assure the quality and integrity of data used in making judgments about the safety of products regulated by the agency. The grounds for disqualification are based on those types of noncompliance that significantly impair achievement of those objectives. Proposed § 3e.202(a) through (p) is deleted, and new § 58.202(a) through (c) clarifies the policy that a testing facility may be disqualified only if the Commissioner finds all three of the following: (1) That the testing facility failed to comply with one or more of the standards set forth in Part 58 or in any other FDA regulations regarding standards for nonclinical testing facilities (e.g., any supplemental requirements in the IND or IDE regulations); (2) that the noncompliance adversely affected the validity of the data produced by the study; and (3) that other lesser regulatory actions, such as warnings or rejection of data from individual nonclinical laboratory studies, have not been or probably will not be adequate to achieve compliance. This

approach will assure that the sanction will not be used in trivial situations, but will be invoked only when the violation has compromised the integrity of a study. It further requires the Commissioner to consider the availability and probable effectiveness of lesser sanctions as an alternative to disqualification. It would not, however, preclude disqualification without prior warning.

As pointed out in the preamble to the proposed regulations, the provisions for disqualification are not to be interpreted as either the exclusive or primary administrative action for noncompliance with good laboratory practice. Disqualification is designed to provide FDA with an enforcement tool that is more efficient and effective than a study-by-study review when it becomes apparent that a testing facility is not capable of producing accurate and valid test results. The disqualification of a nonclinical testing facility will be reserved for the the rare case when the rejection of a particular study is an inadequate regulatory response. The testing facility and/or the sponsor of the nonclinical laboratory study may also be prosecuted for violations of Federal criminal laws, including section 301(e) of the Federal Food, Drug, and Cosmetic Act (failure to make a report required under certain other sections of the act, because a grossly erroneous or inadequate report does not fulfill the statutory obligation) and 18 U.S.C. 1001 (submission of a false report to the government). Even where the testing facility is not under a direct statutory obligation to submit information to FDA, and in fact does not send data to the agency but merely transmits them to the sponsor, the facility is likely to be aware that FDA will be the ultimate recipient. In such cases, it may be liable for aiding and abetting in the violation (18 U.S.C. 2) or for causing the violation to be made by a third party.

233. Two comments stated that the disqualification regulation seemed to apply only to private firms.

This interpretation is incorrect. The preamble to the proposed regulations makes clear the policy that the good laboratory practice regulations are to apply to any institution that generates or otherwise prepares safety data for submission to FDA. Included in that definition, to the extent that they prepare safety data to be submitted to FDA in support of petitions for regulated products, are, for example, veterinary and medical clinics, universities and State experimental stations, and State and Federal Government research laboratories. Accordingly, disqualification provisions apply equally to all facilities that prepare safety data for submission to FDA. The language regarding the intended use of sanctions is incorporated into § 58.202(c).

NOTICE OF AND OPPORTUNITY FOR HEARING ON PROPOSED DISQUALIFICATION

234. Several comments stated that the disqualification process, as proposed, would violate due process, deny a formal hearing, and deny a right of appeal to the courts.

The Commissioner advises, and the revisions to § 58.202 make clear, that the disqualification procedure will not be invoked for minor violations of the regulation. In addition, § 58.204 provides that a regulatory hearing may be conducted in accordance with 21 CFR Part 16. Such a hearing provides all the safeguards essential to due process. See also the FEDERAL REGISTER of 40 FR 40713 et seq. (preamble to Subpart F of 21 CFR Part 2, recodified as 21 CFR Part 16—Regulatory Hearing Before the Food and Drug Administration; section 201(y) of the act (21 U.S.C. 321(y)) (procedural requirements of an "informal hearing"); *Goldberg* v. *Kelly*, 397 U.S. 254 (1970). Judicial review of final administrative action is provided by the Administrative Procedure Act (5 U.S.C. 701 et seq.). See also § 10.45 *Court Review of final administrative action; exhaustion of administrative remedies* (21 CFR 10.45); and 40 FR 40689-40691 (preamble to procedural regulations, § 2.11 (recodified as 21 CFR 10.45)).

235. Several comments expressed the concern that any regulatory hearing conducted under 21 CFR Part 16 should provide for the confidentiality of all data on which the hearing is based.

The Commissioner advises that § 16.60(a) (21 CFR 16.60(a)) provides adequate safeguards when required to maintain the confidentiality of commercial information.

236. One comment stated that if notice for such a hearing should be mailed to a facility, more than 3 days should be allowed for a facility to be able to prepare itself to come to a meeting.

The Commissioner finds that the provisions of § 16.22 (21 CFR 16.22) provide adequate flexibility for any party responding to a notice of opportunity for a hearing. See also the comments addressed to 21 CFR 52.204, set out in the preamble to the proposed regulations on obligations of sponsors and monitors, published in the FEDERAL REGISTER of September 27, 1977 (42 FR 49619).

237. One comment suggested that § 58.204 include a provision specifying that a sponsor be allowed to intervene in the hearing process when a notice of opportunity for a hearing has issued to a testing facility that is performing studies under contract for the sponsor.

Inasmuch as the disqualification process in such a case is directed at the testing facility rather than the sponsor and inasmuch as the alleged violations involved would be those of the testing facility, the Commissioner finds that intervention by a sponsor (or, in many cases, multiple sponsors) would serve no useful purpose. As noted in the preamble to the proposed regulation (41 FR 51218), a sponsor who wishes to contest a finding that a particular study or studies is or are inadequate will be provided an opportunity to do so by the procedures for denying or withdrawing the approval of an application for a research or marketing permit.

238. Concern was also expressed that a reasonable time be provided to allow a sponsor to conduct a new test prior to termination or withdrawal.

The Commissioner emphasizes that in those cases in which a safety decision has been based on data that have subsequently been called into question, protection of the public requires that proceedings be instituted without delay. As previously noted, opportunity to contest a finding that a particular study is so inadequate that it will not support a claim of safety of a product will be provided by procedures set forth in other regulations, e.g., withdrawal of an NDA.

FINAL ORDER ON DISQUALIFICATION

239. Several comments stated that § 58.206 should provide specifically for appeal to the Federal courts following a final decision to disqualify by the Commissioner.

The Commissioner notes that the provisions of 21 CFR 16.120 and 10.45 adequately address this point. These regulations clearly state the provisions that apply to court review of final administrative action.

240. One comment suggested that § 58.206(b) be modified to require that sponsors be notified, when applicable, at the time of issuance of a final order to a testing facility.

The Commissioner advises that such notification, which is discretionary, is expressly provided for in § 58.213(b). Additionally, § 58.206(a) and (b) are revised to reflect the requirement that the Commissioner must make the findings required by § 58.202 before a final order disqualifying a nonclinical testing facility shall issue.

ACTIONS UPON DISQUALIFICATION

241. Several comments objected to the retroactive provisions of § 58.210(a), which state that once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, that contains or relies upon any nonclinical

laboratory study conducted by the disqualified testing facility may be examined to determine whether these studies were or would be essential to a decision.

The Commissioner advises that calling into question studies performed by a subsequently disqualified testing facility does not represent a departure from prior FDA policy in other areas. FDA must make additional inquiries to establish safety any time a question is raised about data previously submitted, regardless of whether a disqualification procedure exists. Section 58.210(a) allows the person relying on the study in question to establish that the study was not affected by the circumstances that led to disqualification. The safety of the public would not be adequately protected were no such validation required when serious questions are raised regarding the adequacy of data upon which regulatory decisions are based.

Section 58.210 is revised by the addition of paragraph (b), which states that no nonclinical laboratory study begun after a facility has been disqualified will be considered in support of any application for a research or marketing permit unless the facility has been reinstated under § 58.219. This addition makes it clear that, in such a case, no subsequent information can be submitted for purposes of subsequent validation. If the facility is reinstated, however, the study might by acceptable to FDA. This provision does not relieve the applicant from any other requirement under FDA regulations that all data and information regarding clinical experience with the article in question be submitted to the agency.

242. Many comments regarding § 58.210 were based on the assumption that the disqualification process might be invoked for a minor violation of the good laboratory practice regulation and stated that calling studies into question based on a minor violation was unreasonable.

As previously discussed, § 58.202 is revised to make it clear that the disqualification process will be reserved for those situations in which lesser sanctions, e.g., rejection of individual studies, will not suffice. Because disqualification will be reserved for use in serious situations, the Commissioner finds that calling into question all studies done before or after disqualification is warranted.

PUBLIC DISCLOSURE OF INFORMATION UPON DISQUALIFICATION

243. Several comments said that proprietary or trade secret documents should not be released. Others urged that disqualification records not be disclosed.

The Commissioner advises that release of all such documents is governed by the provisions of the Freedom of Information Act (5 U.S.C. 552) and 21 CFR Part 20 and need not be separately dealt with in this regulation. Interested parties are referred specifically to Part 20—Public Information (21 CFR Part 20). Section 20.61 (21 CFR 20.61) deals with trade secrets and commercial information and § 20.64 (21 CFR 20.64) deals with investigatory records. The preamble to the public information regulations (39 FR 44602 et seq.) (since recodified as Part 20) discusses these issues at length.

244. One comment on § 58.213 stated that no notification of other government departments or agencies should issue until completion of the judicial process.

The Commissioner disagrees and finds that withholding notification until completion of the administrative process by the agency provides an adequate opportunity for a testing facility to be heard prior to the issuance of any such notification.

245. Another comment stated that because FDA is a Federal agency, notification of State agencies is outside FDA's jurisdiction.

The Commissioner points out that section 705(b) of the act (21 U.S.C. 375(b)) provides for dissemination of information regarding food, drugs, or devices in situations involving imminent danger to health or gross deception of the consumer. In addition, the Commissioner emphasizes that he proposes to notify the States only in those situations for which adequate cause has been established and for which a final order has been issued. Section 58.213(a) is amended to make it clear that such notification shall state that it is given because of the relationship between the testing facility and the person notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified. Additionally, § 58.213 is modified to make it clear that notification of disqualification may be sent by the Commissioner not only to other Federal agencies but to any other person known to have professional relations with the disqualified testing facility. This includes sponsors of studies being performed by the facility.

246. A comment suggested that the scope of notification should be limited to those nonclinical laboratory studies upon which the decision to disqualify was based.

The language of § 58.213 makes it clear that notification may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations. The Commissioner finds that, given the expressed purpose of notification, further limitation would be inappropriate.

ALTERNATIVE OR ADDITIONAL ACTIONS TO DISQUALIFICATION

247. One comment on § 58.215 suggested that informal procedures be used prior to the institution of more formal procedures.

The Commissioner notes that this approach was discussed in the preamble to the proposed regulation at 41 FR 51218. Because such informal procedures have, in the past, doubled the time and expense of all involved parties without discernible benefit, the Commissioner has decided not to provide for informal procedures in these regulations.

SUSPENSION OR TERMINATION OF A TESTING FACILITY BY A SPONSOR

248. Many comments on § 58.217 said that the section seemed to be an attempt on the part of FDA to provide legal grounds for the unilateral breaking of contracts between private parties.

The Commissioner finds that the section, as written, was subject to a great deal of misunderstanding. Therefore, the section is revised. The Commissioner advises that nothing in Part 58 is intended to infringe upon or alter the private contractual arrangements between a sponsor and a nonclinical testing facility. A sponsor may terminate a testing facility for reasons of its own whether or not FDA has begun any action to disqualify that facility. Where a sponsor has independent grounds for suspending or terminating studies performed for that sponsor by the facility under contract, the fact that FDA has not itself disqualified the facility may not be raised by the contract facility as a defense against the sponsor.

249. Several comments said notification within 5 days was impractical.

The Commissioner agrees, and the time period is extended to 15 working days.

250. A number of comments said the notification requirement provided a sponsor with an unfair opportunity to impugn a contract facility that would have no opportunity for response.

The Commissioner emphasizes that termination of a nonclinical testing facility by a sponsor should be subject to the contract between the two parties. A nonclinical testing facility, as a party to the contract, may protect itself from unjust termination by the terms of its contract with the sponsor. Remedies for both parties to such a contract may be spelled out in the contract and are governed by principles of contract law. The Commissioner fur-

ther emphasizes that the requirement that a sponsor notify FDA when it has terminated or suspended a testing facility applies only to those cases in which an application for a research or marketing permit has been submitted. Where no application has been submitted, no notification is required.

REINSTATEMENT OF A DISQUALIFIED TESTING FACILITY

251. One comment on § 58.219 expressed concern that when read with § 58.210, it was confusing.

The Commissioner finds that the addition of § 58.210(b) substantially clarifies the status of studies conducted before, during, and after disqualification and that further amendment is unnecessary.

252. A typographical error in the last sentence of § 58.219 has been corrected. The last sentence now reads: "A determination that a testing facility has been reinstated is disclosable to the public under Part 20 of this Chapter."

CONFORMING AMENDMENTS

253. The Commissioner is adding to or revising provisions in the regulations regarding food and color additives, new drugs for investigational use, new drug applications, OTC drug products, antibiotic drugs, new animal drug applications, biological product licenses, and performance standards for electronic products to incorporate appropriate implementing provisions for, and cross references to, Part 58, which is being added by this document. Each of the regulations requires the submission of data which may include nonclinical laboratory studies. The regulations are being revised to require, with respect to each nonclinical laboratory study contained as part of the submitted information, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. The revisions highlight the fact that although studies not conducted in compliance with the regulations may continue to be submitted to FDA, the burden of establishing that the noncompliance did not affect the quality of the data submitted is on the person submitting the noncomplying study.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701(a), 706, and 801, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360j, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n)) and under authority delegated to him (21 CFR 5.1), the Commissioner amends Chapter I of 21 CFR as follows:

SUBCHAPTER A—GENERAL

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. Part 16 is amended in § 16.1 by redesignating paragraph (b)(30) as paragraph (c) and by adding new paragraph (b)(30), to read as follows:

§ 16.1 Scope.

* * * * * * *

(b) * * *

(30) Section 58.204(b) of this chapter, relating to disqualifying a nonclinical laboratory testing facility.

(c) Any other provision in the regulations in this chapter under which a party who is adversely affected by regulatory action is entitled to an opportunity for a hearing, and no other procedural provisions in this part are by regulation applicable to such hearing.

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2. Part 58 is added to read as follows:

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Sec.
58.1 Scope.
58.3 Definitions.
58.10 Applicability to studies performed under grants and contracts.
58.15 Inspection of a testing facility.

Subpart B—Organization and Personnel

58.29 Personnel.
58.31 Testing facility management.
58.33 Study director.
58.35 Quality assurance unit.

Subpart C—Facilities

58.41 General.
58.43 Animal care facilities.
58.45 Animal supply facilities.
58.47 Facilities for handling test and control articles.
58.49 Laboratory operation areas.
58.51 Specimen and data storage facilities.
58.53 Administrative and personnel facilities.

Subpart D—Equipment

58.61 Equipment design.
58.63 Maintenance and calibration of equipment.

Subpart E—Testing Facilities Operation

58.81 Standard operating procedures.
58.83 Reagents and solutions.
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58.219 Reinstatement of a disqualified testing facility.

AUTHORITY: Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463, as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360j, 371(a), 376, and 381); secs. 215, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n).

Subpart A—General Provisions

§ 58.1 Scope.

This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 706, and 801

of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

§ 58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) "Test article" means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act.

(c) "Control article" means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article other than a test article that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

(d) "Nonclinical laboratory study" means any in vivo or in vitro experiment in which a test article is studied prospectively in a test system under laboratory conditions to determine its safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

(e) "Application for research or marketing permit" includes:

(1) A color additive petition, described in Part 71 of this chapter.

(2) A food additive petition, described in Parts 171 and 571 of this chapter.

(3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.35 of this chapter.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1 of this chapter.

(5) A "Notice of Claimed Investigational Exemption for a New Drug," described in Part 312 of this chapter.

(6) A "new drug application," described in Part 314 of this chapter.

(7) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in Part 330 of this chapter.

(8) Data and information regarding a prescription drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, to be described in this chapter.

(9) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in Part 430 of this chapter.

(10) A "Notice of Claimed Investigational Exemption for a New Animal Drug," described in Part 511 of this chapter.

(11) A "new animal drug application," described in Part 514 of this chapter.

(12) Data and information regarding a drug for animal use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, to be described in this chapter.

(13) An "application for a biological product license," described in Part 601 of this chapter.

(14) An "application for an investigational device exemption," described in Part 812 of this chapter.

(15) An "Application for Premarket Approval of a Medical Device," described in section 515 of the act.

(16) A "Product Development Protocol for a Medical Device," described in section 515 of the act.

(17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in section 513 of the act.

(18) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in section 514 of the act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in Subpart D of Part 1003 of this chapter.

(20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in § 1010.4 of this chapter.

(22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in § 1010.5 of this chapter.

(f) "Sponsor" means:

(1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study;

(2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

(3) A testing facility, if it both initiates and actually conducts the study.

(g) "Testing facility" means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. "Testing facility" includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. "Testing facility" encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

(h) "Person" includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

(i) "Test system" means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. "Test system" also includes appropriate groups or components of the system not treated with the test or control articles.

(j) "Specimen" means any material derived from a test system for examination or analysis.

(k) "Raw data" means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

(l) "Quality assurance unit" means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

(m) "Study director" means the individual responsible for the overall conduct of a nonclinical laboratory study.

(n) "Batch" means a specific quantity or lot of a test or control article that has been characterized according to § 58.105(a).

§ 58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

§ 58.15 Inspection of a testing facility.

(a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.

Subpart B—Organization and Personnel

§ 58.29 Personnel.

(a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

(b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

(c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

(e) Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

(f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

§ 58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

(a) Designate a study director as described in § 58.33, before the study is initiated.

(b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study, and document and maintain such action as raw data.

(c) Assure that there is a quality assurance unit as described in § 58.35.

(d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

(e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

(f) Assure that personnel clearly understand the functions they are to perform.

(g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

§ 58.33 Study director.

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall assure that:

(a) The protocol, including any change, is approved as provided by § 58.120 and is followed.

(b) All experimental data, including observations of unanticipated responses to the test system are accurately recorded and verified.

(c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.

(d) Test systems are as specified in the protocol.

(e) All applicable good laboratory practice regulations are followed.

(f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

§ 58.35 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit composed of one or more individuals who shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(b) The quality assurance unit shall:

(1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, name of the sponsor, name of the study director, and status of the final report.

(2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible.

(3) Inspect each phase of a nonclinical laboratory study periodically and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for re-inspection. For studies lasting more than 6 months, inspections shall be conducted every 3 months. For studies

Federal Register

FRIDAY, DECEMBER 22, 1978
PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

[4110-03-M]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 76N-0400]

NONCLINICAL LABORATORY STUDIES

Good Laboratory Practice Regulations

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The agency is issuing final regulations regarding good laboratory practice in the conduct of nonclinical laboratory studies. The action is based on investigatory findings by the agency that some studies submitted in support of the safety of regulated products have not been conducted in accord with acceptable practice, and that accordingly data from such studies have not always been of a quality and integrity to assure product safety in accord with the Federal Food, Drug, and Cosmetic Act and other applicable laws. Conformity with these rules is intended to assure the high quality of nonclinical laboratory testing required to evaluate the safety of regulated products.

EFFECTIVE DATE: June 20, 1979.

FOR FURTHER INFORMATION CONTACT:

Paul D. Lepore, Bureau of Veterinary Medicine (HFV-102), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, (301-443-4313).

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) is establishing regulations in a new Part 58 (proposed as Part 3e) in Title 21 (21 CFR Part 58) regarding good laboratory practice. These constitute the first of a series of regulations concerning investigational requirements which are being developed as a result of the FDA Bioresearch Monitoring Program. Proposed regulations, providing interested persons 120 days to submit comments, were published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206). In addition, public hearings were held on February 15 and 16, 1977 for the presentation of oral testimony on the proposal. Twenty-two oral presentations were given (transcripts are on file with the Hearing Clerk, Food and Drug Administration), and 174 written comments were received. The comments have been categorized and include the following: manufacturers of regulated products (64), associations (40), medical centers (20), private testing or consulting laboratories (18), educational institutions (15), government agencies (8), individuals (8), and an airport director (1).

In the proposal, regulations were designated as a new Part 3e. This final rule incorporates them into a new Part 58 (21 CFR Part 58). The following redesignation table correlates the new sections with those proposed, and, in most instances, reference to the new sections will be used hereinafter.

New Section	*Old Section*
Subpart A	
58.1	3e.1
58.3	3e.3
58.10	3e.10
58.15	3e.15
Subpart B	
58.29	3e.29
58.31	.....
58.33	3e.31
58.35	3e.33
Subpart C	
58.41	3e.41
58.43	3e.43
58.45	3e.45
58.47	3e.47
58.49	3e.49
58.51	3e.51
58.53	3e.53
Subpart D	
58.61	3e.61
58.63	3e.63
Subpart E	
58.81	3e.81
58.83	3e.83
58.90	3e.90
Subpart F	
58.105	3e.105
58.107	3e.107
58.113	3e.113
Deleted	3e.115
Subpart G	
58.120	3e.120
58.130	3e.130
Subpart J	
58.185	3e.185
58.190	3e.190
58.195	3e.195
Subpart K	
58.200	3e.200
58.202	3e.202
58.204	3e.204
58.206	3e.206
58.210	3e.210
58.213	3e.213
58.215	3e.215
58.217	3e.217
58.219	3e.219

As a part of the overall bioresearch monitoring program that was described in the proposal, a pilot inspection program was carried out to assess the current status of laboratory practice of nonclinical testing facilities to aid in evaluating the relevance of the proposed regulations, and to identify any unanticipated difficulties in implementing an agency-wide monitoring and compliance program for the testing facilities.

The pilot inspection program began in December of 1976 and covered a representative sample of testing facilities. The results of these inspections have been evaluated, and the results of the analysis have been made available to the public as OPE Study 42, "Results of the Nonclinical Toxicology Laboratory Good Laboratory Practices Pilot Compliance Program." Notice of availability of this report was published in the FEDERAL REGISTER of October 28, 1977 (42 FR 56799).

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Conduct of a nonclinical laboratory study results (paragraphs 205 through 209).

Records and Reports

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Alternative or additional actions to disqualification (paragraph 247).
Suspension or termination of a testing facility by a sponsor (paragraphs 248 through 250).
Reinstatement of a disqualified testing facility (paragraphs 251 through 252).

Conforming Amendments (paragraph 253)

GENERAL ISSUES

1. Many of the written responses to the proposal were in two parts: a discussion of broad issues and a critique of the regulations by section and paragraph. Over a thousand individual items have been considered.

2. Thirty-two comments requested republication of the proposed regulations as guidelines.

The Commissioner of Food and Drugs advises that publishing guidelines rather than regulations was considered and rejected before publication of the proposal. The question was considered again in preparation of this order, and again rejected. The seriousness of problems encountered in testing facilities demands the use of an approach that will achieve compliance directly and promptly. Only by specifying the requirements for compliance in detailed, enforceable regulations can the Commissioner be assured of the quality and integrity of the data submitted to the agency in support of an application for a research or marketing permit.

3. Some comments objected to the incorporation by reference of other laws, recommendations, and guidelines as being either redundant or without the authority conferred by rulemaking procedures as required by the Administrative Procedure Act. It was also asserted that such incorporation could lead to confusion.

The Commissioner agrees that these regulations should not duplicate regulations and requirements subject to the purview of other agencies. Therefore, reference to animal care provisions of the Animal Welfare Act of 1970 (Pub. L. 91-570) and recommendations contained in Department of Health, Education, and Welfare (HEW) Publication No. (NIH) 74-23 have been deleted from §§ 58.43(a) and 58.90(a) (21 CFR 58.43(a) and 58.90(a)). Also, all provisions that referred to regulations of the Occupational Safety and Health Administration or were concerned with the health and safety of employees have been revised or deleted, i.e., 21 CFR 58.33(a) (by deletion of proposed 21 CFR 3e.31(a)(11)), 21 CFR 58.53(b), 21 CFR 58.81 (by deletion of proposed 21 CFR 3e.81(b)(10)), and 21 CFR 58.120(a) (by deletion of proposed 21 CFR 3e.120(a)(17)). Reference to the regulations of the Nuclear Regulatory Commission has been removed from § 58.49; and proposed § 3e.115, dealing with the handling of carcinogenic substances, has been deleted. In addition, the Commissioner has deleted reference to the various animal care guideline cited in the proposal.

4. Some comments said the regulations should not be retroactive to previous studies or those ongoing and should include reasonable transitional provisions for their implementation.

To give nonclinical laboratory facilities adequate time to implement required changes in their organization and physical plant, a period of 180 days after publication in the FEDERAL REGISTER is provided for these regulations to become fully effective. The regulations are not retroactive. All studies initiated after the effective date shall be subject to the regulations. The remaining portions of studies in progress on the effective date of the regulations shall be conducted in accordance with these regulations.

5. A number of comments challenged the general legal authority of FDA to issue good laboratory practice regulations. Other comments challenged the legal authority to require record retention or quality assurance units, or to specify the content of required records or location of storage.

The Commissioner finds that the authority cited in the preamble to the proposal (41 FR 51219; Nov. 19, 1976) provides a sound legal basis for the regulations. Although many matters covered in these regulations are not explicitly mentioned in any of the laws administered by the Commissioner, the Supreme Court has recognized, in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973), that FDA has authority that "is implicit in the regulatory scheme, not spelled out *in haec verba*" in the statute. As stated in *Morrow* v. *Clayton*; 326 F.2d 36, 44 (10th Cir. 1963):

> However, it is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning* v. *Family Publications Service, Inc.*, 411 U.S. 356 (1973); see also *National Petroleum Refiners Association* v. *F.T.C.*, 482 F.2d 672 (D.C. Cir. 1973). The Commissioner concludes that there is ample authority for the promulgation of good laboratory practice regulations. No comment presented any explanation or information to the contrary, let alone a cogent argument that FDA lacks legal authority under existing statutes. The standards prescribed represent amplification of the legal requirements regarding evidence of safety necessary to approve an application for a research or marketing permit and parallel, to a great extent, steps that FDA has found have been taken by members of the regulated industry to improve nonclinical laboratory operations.

6. One comment argued that the opinion of the Court of Appeals in *American Pharmaceutical Association* v. *Weinberger*, 530 F.2d 1054 (D.C. Cir. 1976), should be read to limit FDA's authority to issue regulations under section 701(a) of the act (21 U.S.C. 371(a)).

The Commissioner disagrees with the argument advanced in the comment. As discussed in the preamble to the proposed regulation, the agency's authority to issue regulations under section 701(a) of the act has been upheld by the courts. (See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *National Confectioners Association* v. *Califano*, No. 76-1617 (D.C. Cir. Jan. 20, 1978); *Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).) The question is not FDA's authority to issue regulations under section 701(a) of the act per se, but whether regulations issued under section 701(a) of the act appropriately implement other sec-

tions of the act. As articulated in the original proposal, and as discussed in the previous two paragraphs, the Commissioner has determined that these regulations are essential to enforcement of the agency's responsibilities under sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act, as well as the responsibilities of FDA under sections 351 and 354-360F of the Public Health Service Act.

7. A number of comments said various sections of the act did not specify the submission of safety data or did not deal with "applications for research or marketing permits."

The Commissioner has reviewed the comments and finds that the comments are based on a misunderstanding of the phrase, "applications for research or marketing permits." This concept is discussed in relation to § 58.3(e) below. Each cited provision contains authority for FDA either to require submission of, or to use, nonclinical safety data to justify a decision to approve the distribution of a regulated product.

8. A number of comments said the cost of implementing the proposed regulations would be prohibitive to smaller testing laboratories and would, at the least, result in a substantial increase in the cost of product testing.

The Commissioner agrees that implementation of these regulations will increase the cost of nonclinical laboratory testing. The Commissioner finds, however, that such costs are justified on the basis of the resultant increase in the assurance of the quality and integrity of the safety data submitted to the agency. The agency has previously concluded (see the FEDERAL REGISTER of November 19, 1976 (41 FR 51220)) that this document does not contain regulations requiring preparation of an inflation impact statement under Executive Orders 11821 and 11929, Office of Management and Budget Circular A-107 and the guidelines issued by the Department of Health, Education, and Welfare. For a notice on the availability of the agency's economic impact assessment regarding rules for good laboratory practice for nonclinical laboratory studies, see the FEDERAL REGISTER of February 7, 1978 (43 FR 5071). The revisions in this final rule, along with the findings of the pilot program, which showed that many of the inspected facilities were already substantially in compliance with the proposed regulations, should allay some of the concerns of small facilities regarding cost or feasibility of compliance.

9. Many comments suggested changes in language, grammar, terminology, punctuation; sentence structure, and other editorial changes to clarify or improve upon the requirements as stated in the regulations or to eliminate redundancies or inconsistencies. Comments that raised significant policy questions, suggested changes in the substance of the regulation, or otherwise required, in the Commissioner's opinion, a specific response, are discussed individually below. Many of the suggested changes, however, were editorial and stylistic and do not warrant a detailed discussion.

The Commissioner has reviewed each of these numerous editorial and language changes to determine whether it offered an improvement in clarity or definition, eliminated an obvious error or redundancy, promoted consistency with other portions of the regulations, or otherwise identified textual problems that had not been previously noted by FDA. Where the proposed alternative language or other changes suggested by the comments were superior to the proposal, they were adopted in substance or verbatim. Where they did not offer any improvement, the Commissioner declined to accept them.

GENERAL PROVISIONS

SCOPE

10. Numerous comments addressed the stated scope of the proposed regulations (§ 58.1). Six comments said the proposed scope was vague. Ten comments said the scope should be limited to long-term animal toxicity studies. Twenty-two comments indicated that the scope should be limited to animal safety studies to be submitted to FDA. Individual comments recommended limiting the scope to studies performed on marketed products, studies performed on animals and other biological test systems, or studies submitted in support of a color additive petition, food additive petition, investigational new drug application, new drug application, or new animal drug application.

In the preamble to the proposed regulations, the Commissioner set forth the reasons for the broad terminology employed in the statement of scope, stating "these regulations are intended to ensure, as far as possible, the quality and integrity of test data that are submitted to FDA and become the basis for regulatory decisions made by the Agency." In the proposed rule (41 FR 51210), the Commissioner specifically invited comments on which laboratories and/or studies should be subject to the regulations, and further, on whether the scope of the regulations should be defined in terms of the type of testing facility rather than the type of study performed. Based on the review of the comments, the Commissioner has chosen to describe the scope of the regulations in language that is only slightly changed from the proposal. Further clarification of scope is achieved by the specific definition of the key terms, "nonclinical laboratory study" and "application for research or marketing permit" in § 58.3. Taken together, these provisions eliminate any vagueness in the scope of these regulations.

The Commissioner has rejected the request to narrow the scope by listing in the regulation specific types of studies covered. Any such list, if it included all types of studies used by the agency to assess the safety of all the products it regulates, would be cumbersome and might exclude specific types of studies that could become important to future safety decisions. The Commissioner emphasizes that this decision does not mean, however, that the scope of the regulations is unlimited. The scope of the GLP regulations is limited in several ways.

First, they apply only to nonclinical laboratory studies that are submitted or are conducted for submission to the agency in support of a research or marketing permit for a regulated product. Language has been added that provides that the scope includes studies "intended" to support applications for research or marketing permits. This language was included in the preamble to the proposed regulation (41 FR 51209), and the Commissioner has added the language to the regulation because it helps to make clear in advance when a study should comply with the regulation and when a study should be listed on a testing facility's master schedule sheet as a nonclinical laboratory study subject to these regulations (§ 58.35(b)(1)). Tests never intended to be submitted to the agency in support of (i.e., as the basis for) the approval of a research or marketing permit, such as exploratory safety studies and range-finding experiments, are not included even though they may be required to be submitted as part of an application or petition.

Second, the definition of "nonclinical laboratory study" (§ 58.3(d)) makes it very clear that studies utilizing human subjects, clinical studies, or field trials in animals are not included.

Third, the scope of coverage is now limited to safety studies, i.e., those which can be used to predict adverse effects of, and to establish safe use characteristics for, a regulated product. "Functionality studies" have been excluded in the final rule.

Fourth, the definition of "test system" (§ 58.3(i)) taken together with the definition of "nonclinical laboratory study" makes it clear that the scope of coverage is confined to studies performed on animals, plants, microorganisms or subparts thereof.

Products regulated by the agency, for which safety data may be required,

cover a wide range of diverse items that pose quite different types of risk. Examples include implantable medical devices; indirect food additives which may occur in food in very small quantities; direct food additives which may be consumed on a daily basis in larger quantities; human drugs intended for prescription or over-the-counter use; animal drugs intended for use in pets and other companion animals of social importance, drugs used in food-producing animals (drug residues can become a part of food); radiation products used in the diagnosis and/or treatment of a disease or condition; radiation products (e.g., microwave ovens and television sets) widely used by the public; vaccines; and blood components and derivatives.

The guarantee of the safety of each of these product classes requires conducting a broad spectrum of safety tests, all of which should be subject to the same standards. Therefore, the Commissioner rejects the proposal to limit the scope of these regulations to long-term animal toxicity studies. Median lethal dose (LD_{50}) and other short-term tests are covered by the regulations because they may serve as part of the basis for approval of, for example, use of an indirect food additive or an investigational new drug in man.

In vitro biological tests are included insofar as such tests have a bearing on product safety, even though they are not now used in agency decisions, because they may in the future become important indicators of safety. Examples of such tests include short-term mutagenicity tests as well as various other tissue culture and organ tests.

Also included in the scope of these regulations are studies of safety of regulated products on target animals, acute toxicity studies on a final product formulation, studies of test articles that are completed in 14 days or less, studies conducted on test articles used in "minor food producing species of animals," and studies on test articles which are not widely used.

11. Several comments closely related to the concerns expressed in paragraph 10 of this preamble requested that further language be added to the regulation exempting certain specific types of studies from coverage.

The Commissioner has reviewed the requests and has chosen not to change the language of the regulation itself to exclude specific study types other than those already mentioned (e.g., studies utilizing human subjects). The regulations apply to any study conducted to provide safety data in support of an application for a research or marketing permit for an FDA-regulated product, and a specific type of study which may be important in the overall safety evaluation of one type of regulated product may not be important in evaluating another. The Commissioner believes it useful to identify in this preamble further examples of studies that are—or are not—within the scope of the GLP regulations.

Examples of studies that are not within the scope of these GLP regulations include:

a. Clinical tests performed solely in conjunction with product efficacy.

b. Chemical assays for quality control.

c. Stability tests on finished dosage forms and products.

d. Tests for conformance to pharmacopeial standards.

e. Pharmacological and effectiveness studies.

f. Studies to develop new methodologies for toxicology experimentation.

g. Exploratory studies on viruses and cell biology.

h. Studies to develop methods of synthesis, analysis, mode of action, and formulation of test articles.

i. Studies relating to stability, identity, strength, quality, and purity of test articles and/or control articles that are covered by good manufacturing practice regulations.

Further examples of types of tests not covered include:

a. Food additives: Tests of functionality and/or appropriateness of the product for its intended use; tests of extractability of polymeric materials that contact food; and all chemical tests used to derive the specifications of the marketed product.

b. Human and animal drugs: Basic research; preliminary exploratory studies; pharmacology experiments; studies done to determine the physical and chemical characteristics of the test article independent of any test system; and clinical investigations.

c. Medical devices: All studies done on products that do not come in contact with or are not implanted in man.

d. Diagnostic products: Essentially all are excluded.

e. Radiation products: Chemical and physical tests.

f. Biological products: All tests conducted for the release of licensed biologicals described in Part 601 (21 CFR Part 601) of this chapter.

These examples do not represent all the exclusions from the regulations, but provide guidance in applying the agency's safety considerations to specific situations. The defined scope of the regulations is necessarily broad to encompass the wide range of types of safety tests, types of testing facilities and regulated products for which proper safety decisions are important.

12. More than 20 comments sought the addition of specific language exempting various classes of FDA-regulated products, such as medical devices, from coverage by the regulations.

The Commissioner has generally elected not to permit exemptions based on broad categories of regulated products because no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another. Proper safety decisions are important for all these products; accordingly, the processes by which such safety data are collected should be subjected to identical standards of quality and integrity.

13. Several comments said that the animal care provisions should apply only to these nonclinical studies using laboratory animals and should not apply to nonclinical studies which involve large animals.

It is clear that the animal care provisions are directed toward the use of laboratory animals, and therefore certain of these provisions may not apply to studies not involving laboratory animals, such as tissue residue and metabolism studies conducted in cattle. Although these studies do fall within the definition of a nonclinical laboratory study, the animals used in such a study are not generally kept in a laboratory setting. Because the husbandry requirements for laboratory animals differ greatly from those for large animals, the agency does not require that large animals be reared and maintained under the same conditions as laboratory animals. The regulations are revised to include terms such as "when applicable" and "as required" in those provisions for which a wide latitude of acceptable husbandry practice exists.

14. Three comments said the regulations should apply to all studies whether submitted in support of or as a challenge to an "application for a research or marketing permit."

The Commissioner agrees, in principle, that all nonclinical studies should be performed in a manner designed to ensure the quality and integrity of the data. FDA is requiring that, at the time a study is submitted, there be included with the study either a statement that the study was conducted in compliance with Part 58 requirements or, if the study was not conducted in compliance with those requirements, a statement that describes in detail all deviations. This requirement means that, at the time a study not conducted in compliance with the requirements is submitted, the agency may evaluate the effects of the noncompliance and take one of the following actions: (1) Determine that the noncompliance did not affect the validity of the study and accept it, or (2) determine that the noncompliance may have affected the validity of the study

and require that the study be validated by the person submitting it, or (3) reject the study completely. The standard of review applied to studies that contain data adverse to a product is no different. That is, a study that failed to comply with these regulations might, nonetheless, contain valid and significant data demonstrating a safety hazard. Thus, FDA is not proposing a double standard, but is, rather, seeking to address those studies that present the most serious regulatory problems.

The preamble to the proposed regulation (41 FR 51215) discussed this issue as follows:

> Valid data and information in an otherwise unacceptable study which are adverse to the product, however, may serve as the basis for regulatory action.
>
> This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard. It reflects current agency policy; even in situations where the scientific quality of an investigational drug study is not in question, FDA may receive data but not use it in support of a decision to approve testing or commercial distribution because of ethical improprieties in the conduct of the study. (See 21 CFR 312.20).

A positive finding of toxicity in the test system in a study not conducted in compliance with the good laboratory practice regulations, may provide a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that scientifically valid results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product. The treatment of studies conducted by a disqualified testing facility is discussed in paragraph 231a. below.

15. Exemptions from coverage by these regulations were requested for various types of facilities. Requests were received that they not apply to academic, medical, clinical, and not-for-profit institutions.

The public health purpose of these regulations applies to all laboratory studies on which FDA relies in evaluating the safety of regulated products, regardless of the nature of the facilities in which the studies are conducted. The Commissioner finds that granting an exemption based on type of facility would frustrate the intent of the good laboratory practice regulations. Many other comments urged that such exemptions not be considered because the standards applied to nonclinical testing should be uniform. Many of the requests for exemption were based on the idea that academic or not-for-profit institutions conduct primarily basic research and ought, therefore, to be specifically excluded. Insofar as academic institutions are concerned, the Commissioner notes that such institutions conduct significant amounts of commercial testing pursuant to contracts. He also notes that significant levels of noncompliance with GLP requirements have been found in such institutions. Moreover, as noted in paragraph 11, basic research on drugs is outside the scope of these regulations. In short, no justification has been presented to warrant granting an exemption to such a facility, and any such exemption from the regulations by the type of facility collecting safety data would not provide equal application of the principles of good laboratory practice. Product safety decisions are equally important whether data are collected by the largest commercial nonclinical laboratory facility or by the smallest nonprofit facility. Therefore, the data collected in all types of facilities should be subjected to the same standards of quality and integrity. The results of the pilot program show that the proposed regulations represent achievable standards.

16. Exemption of or different standards for studies conducted outside the United States were requested.

These regulations are designed to protect the public health of the American people by assuring the scientific integrity and validity of laboratory studies that the agency relies on in evaluating the safety of regulated products. The same assurance is needed, whether the studies relied on are foreign or domestic in origin. The Commissioner notes that FDA clearly may refuse to accept studies from any nonclinical testing facility, foreign or domestic, that does not follow the requirements set forth in these regulations. To exempt from the requirements imposed on studies conducted in domestic testing facilities a nonclinical study conducted in a testing facility outside the United States that is submitted to FDA in support of an application for a research or marketing permit or to impose different standards for such studies, would only have the effect of discriminating against U.S. firms. Although inspection of a foreign facility may not be made without the consent of that facility, FDA will refuse to accept any studies submitted by any facility that does not consent to inspection. These same conditions apply to other FDA regulations, e.g., the current good manufacturing practice regulations (21 CFR Part 210). a program of inspection of foreign facilities for compliance with those regulations has been conducted by FDA for several years. A similar inspection program of foreign laboratory facilities conducting studies within the scope of this regulation will be conducted; several foreign laboratories were inspected during the pilot program, and mechanisms for such inspections are being worked out with representatives of the responsible regulatory authorities in foreign countries.

DEFINITIONS

The Commissioner received hundreds of comments regarding definitions (§ 58.3). General comments are listed immediately below; comments regarding specific definitions follow in numerical order.

17. Several comments asked that commonly used terms such as "batch," "area," "laboratory," "pathologist," "quality data," "data integrity," "supervisor," and "management" be defined or clarified.

The Commissioner finds that, with the exception of "batch," the terms set out above do not require individual definitions. The term "pathologist" is used in its ordinary sense, as are the terms "supervisor" and "management" and the phrases "quality data" and "data integrity." As a general rule, the regulation defines separately only those words which will be used in a sense which differs from that given in currently accepted dictionaries or words whose meaning will be limited by the regulation. A new definition has been added for the term "batch" because it is used in these regulations in a context different from other agency regulations, e.g., the good manufacturing practice regulations. "Batch" in these regulations means a specific quantity of a test or control article that has been characterized according to § 58.105(a).

18. Several comments on § 58.3(b) questioned the applicability of the term "test substance" to medical devices, radiation products, in vitro diagnostic products, and botanical materials.

The Commissioner has reviewed the comments carefully and finds that many of the comments submitted regarding the term "test substance" argued that the term, as defined, did not accurately reflect the scope intended to be covered. Because the term "substance," in common usage, refers to chemical compounds and biological derivatives of more or less defined composition, and because the term is not commonly understood to include devices or electronic products, the Commissioner has changed the term "test substance" to "test article." The term "article" is intended to include all regulated products which may be the subject of an application for a research or marketing permit as defined in § 58.3(e).

The Commissioner has deleted the reference to botanical materials because all botanical materials subject to

FDA jurisdisction are adequately encompassed by the other articles specifically mentioned in the definition.

19. Clarification of the term "control substance" (§ 58.3(c)) was requested. Several comments asked whether the term was to include carrier substances and solvents and vehicles. Other comments sugested this term could be confused with the same term used by the Drug Enforcement Administration.

The term is changed to "control article" to parallel the revised definition for test article. This change avoids any potential conflict with definitions used by other agencies. The term is intended to define those materials given to control groups of test systems for establishing a basis of comparison. The Commissioner recognizes that for certain nonclinical laboratory studies, no control groups are used, and therefore this definition would not apply. For example, testing the safety of implantable pacemakers in animals would require either no control animals or animals that have only been "sham-operated." The definition includes carrier materials when such carrier materials are given to control groups within test system and likewise for administered vehicles and solvents. The term also applies to articles used as positive controls.

20. Many comments on § 58.3(d) addressed the definition of the term "nonclinical laboratory study." A great many, if not the majority, of the comments sought to change the definition by adding language excluding certain specific tests, products, or types of laboratories.

The Commissioner notes that many of these comments overlap with or are identical to comments submitted in response to § 58.1 (Scope). To the extent that the comments and issues are the same, they have been dealt with in the discussion of § 58.1, above. Other comments are dealt with specifically below.

21. Many comments stated that the proposed language which included studies intended to assess the functionality and/or effectiveness of a test article should be deleted. One comment stated that efficacy testing in nonclinical tests is, by definition, preliminary and should be excluded to be consistent with the scope defined in § 58.1. Other comments stated that the language was too broad and too ambiguous and could be interpreted to include many studies which were not safety studies at all.

The Commissioner has considered these comments and agrees that the language related to functionality and/or effectiveness is too broad. He has, therefore, deleted the sentence.

22. Several comments requested that the last sentence of § 58.3(d) be modified by deleting the proposed examples of tests.

The Commissioner finds that the examples included in the proposal tended to confuse rather than clarify. The examples, therefore, have been deleted.

23. Section 58.3(e), which defines the various types of submissions to FDA, was criticized for use of the term "application for research or marketing permit." Several comments said the term was misleading because not all products are regulated through the use of "permits."

The Commissioner believes the term is appropriate for the purpose of these regulations. As stated in the proposal, this definition includes all the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing marketing of a product. The term is intended solely as a shorthand way of referring to the separate categories of data (identified in the proposal) that are now, or in the near future will become, subject to requirements for submission to the agency.

24. One comment stated that proposed § 3e.3(e)(14) should be deleted because the language was overly broad and because it contradicted the intent expressed in the preamble to limit GLP regulations to safety studies.

The Commissioner notes that the preamble to the proposal (41 FR 51209) stated that studies conducted to determine whether a drug product conforms to applicable compendial and license standards were excluded from the regulation. Safety data submitted to obtain the initial licensing of a biological product are covered by these regulations in § 58.3(e)(13). Once a biological is licensed, however, it becomes subject to testing procedures similar to compendial testing procedures. The Commissioner finds that postlicensing testing of biologicals is conducted more for quality control purposes than for establishing the basic safety of the biologic product and has, accordingly, deleted postlicensing testing from the definition of research and marketing permit.

25. Several comments stated that in vitro diagnostic tests (proposed § 3e.3(e)(15)) should not be included because in vitro diagnostic products do not come in contact with patients and do not, therefore, require preliminary animal safety testing.

Because in vitro diagnostic products do not require any nonclinical laboratory tests for agency approval, the Commissioner agrees that in vitro diagnostic products need not be included in the definition "application for a research or marketing permit." Proposed § 3e.3(e)(15) has, therefore, been deleted from the final regulation.

26. Several comments objected to the inclusion of medical devices in § 58.3(e) (16), (17), and (18), stating that medical devices were not "test substances," that medical devices should not be included because the rules for data submission for such devices were as yet undefined, and that inclusion of medical devices would be unduly restrictive. These comments suggested either total or partial exclusion from coverage under the good laboratory practice regulations.

For reasons stated previously, the Commissioner does not agree that medical devices, as a category, should be excluded. Implantable devices may be composed of polymeric materials that contain components capable of leaching from the device into the body of the recipient or may themselves be adversely affected by body constituents. In either case, safety studies would be necessary to demonstrate that components of the device did not cause harm or that the body constituents did not promote breakdown or malfunction of the device.

27. Comments also requested deletion of all terms relating to radiation products in § 58.3(e) (20), (21), and (22), stating that to include such products would restrict experimentation unduly, and arguing that radiation products were not "test substances."

The Commissioner rejects these comments. The quality and integrity of the safety data are no less important for radiation products than they are for other agency-regulated products. He does not agree that including radiation products will unduly restrict experimentation. The remaining argument is covered in the discussion of "test article" above. A new paragraph § 58.3(e)(19) is added to cover data and information regarding an electronic product submitted as part of the procedure for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation performance standard, described in Subpart D of Part 1003 (21 CFR Part 1003).

28. Many comments stated that the term "sponsor" in § 58.3(f) was too broadly defined. For example, two comments stated that the definition, as written, would cover a company which provides a grant to a university, a fact which, if true, would inhibit giving grants. One comment said that the definition is so broad that it could be interpreted to apply to stockholders.

The Commissioner advises that a person providing a grant may be a sponsor. In the area of nonclinical laboratory studies, most grantors ulti-

mately submit the data to the agency. The Commissioner does not agree that because the definition of "sponsor" includes grantors it will inhibit the giving of grants. No data were submitted to support this argument. The Commissioner further advises that the definition does not include stockholders.

29. Other comments on § 58.3(f) asked whether the regulation allowed for multiple sponsors and whether government agencies could be sponsors.

"Person," as defined in § 58.3(h), includes government agencies, partnerships, and other establishments such as associations. Therefore, a government agency can clearly be a sponsor. In addition, the Commissioner advises that the definition does not preclude joint sponsorship of a study.

30. Several comments asked that the definition of "testing facility" in § 58.3(g) be revised to indicate clearly that a facility conducting a study subject to the regulations should be subject only to the extent that the facility is involved with and responsible for the study.

The Commissioner concludes that no revision to the definition is necessary. The definition clearly does indicate that a facility is covered by the regulations only to the extent that the facility is conducting or has conducted nonclinical laboratory studies.

31. Numerous comments addressed the definition of "test system" in § 58.3(i). Eighteen comments stated that the definition, as written, could be interpreted to require testing of beakers and test tubes. Two comments pointed out that the "test system" is not the container being tested for extractables, but rather it is the animal, microorganism, or cellular components used to test the extractables for safety.

The Commissioner has carefully reviewed the proposed definition in light of the comments and has made a number of changes. The terms "cellular and subcellular" have been replaced for clarity with "subparts thereof" which refers to animals, plants, and microorganisms. The revised definition now reads: "'Test system' means any animal, plant, microorganism, or subparts thereof, to which the test or control article is administered or added for study. 'Test system' also includes appropriate groups or components of the system not treated with the test or control articles." The revisions should make the definition clearly consistent with § 58.3(d) ("nonclinical laboratory study"), which states that studies to determine physical or chemical characteristics of a test article or to determine potential utility are not included. Therefore, testing of beakers and test tubes, which fall into the category of physical and chemical tests, is excluded.

32. Section 58.3(j), which defines "specimen," drew several comments. These included requests for precise definition of the terms "material" and "tissue" and requests for a clearer definition of the term "specimen."

The Commissioner is modifying the term "specimen" to include any material derived from a test system for examination or analysis. Under these circumstances, blood, serum, plasma, urine, tissues, and tissue fractions are all included if they are intended for further examination or analysis. The definition includes all materials that yield data related to the safety decision on a regulated product.

33. Many comments were received on the definition of "raw data" in § 58.3(k). Included were requests to clarify the term "certified" and to state whether carbons, photocopies, and written reports of dictated material could be classified as "raw data". Other issues concerned whether financial information and first drafts of reports were "raw data."

The Commissioner concludes that the proposed definition should be clarified. The word "exact" is substituted for the word "certified." "Certified" connotes a legal document that requires notarization; "exact" has no such connotation and more precisely reflects the Commissioner's intention. The definition is further clarified by inserting, after the first sentence, a new sentence which reads: "In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data." This clarification will permit data collection by tape recorders without requiring the retention of the original tapes. Carbons and photocopies satisfy the regulations, provided they are exact and legible copies of the original information. Neither financial information nor first drafts of reports are raw data within the meaning of the term.

34. Several comments said only recorded data contributing substantially to the study should be retained and, similarly, only computer printouts contributing substantially should be retained. Several comments requested clarification of the method for storing machine-generated data and definition of "on line data recording system."

Because the parenthetical example ("derived from on-line data recording systems") served more to confuse than to clarify, it has been deleted. However, an "on line data recording system" pertains to an instrument that can feed data directly into a computer that analyzes and stores the information. The product of this activity usually consists of a memory unit plus a computer program for extracting the information from the unit. Hard-copy computer printouts are unnecessary, provided the computer memory and program are accompanied by a procedure that precludes tampering with the stored information.

The Commissioner cannot agree that only those portions of the data that contribute substantially to the study need to be retained. Such an approach would require a judgment to be made which, if in error, could lead to improper or incorrect study reconstruction. The purpose of retaining the raw data is to permit the quality assurance unit and agency investigators to reconstruct each phase of a nonclinical laboratory study. Discarding essential records would frustrate this purpose. Raw data may be stored in separate areas provided the archival indexes give the data location.

35. Many comments addressed "quality assurance unit" in § 58.3(l).

The Commissioner has reviewed these comments and concludes that they are more concerned with the concept of the quality assurance unit than with the definition. The comments are therefore dealt with in detail in that section of the preamble concerned with § 58.35 of the regulations. (See paragraphs 75 through 92 below.)

36. Several comments addressed "study director" in § 58.3(m). These comments requested clarification, permission to have more than one study director per study, and that the term "implementation" be changed to "conduct."

The Commissioner has revised the definition to read: "'Study Director' means the individual responsible for the overall conduct of a nonclinical laboratory study." The revision is intended to emphasize that the study director is responsible for the entire study, as well as being responsible for the interpretation, analysis documentation, and reporting of results.

The Commissioner concludes that the other comments received on the definition of "study director" addressed the concept rather than the definition, and these comments are dealt with under the discussion of § 58.33 (see paragraphs 59 through 74, below).

APPLICABILITY TO STUDIES PERFORMED UNDER GRANTS AND CONTRACTS

37. Two comments requested revision of § 58.10 to specify clearly that the sponsor is ultimately responsible for data validity, even if the data are obtained by a sponsor from a grantee or contractor.

The Commissioner concludes that no revision of § 58.10 is necessary. All persons involved in a nonclinical laboratory study are responsible for part or all of the study, depending upon the extent of their participation. Athough a sponsor who submits studies to FDA bears the responsibility for the work performed by a subcontractor or grantee, that fact in no way relieves a grantee or subcontractor from individual responsibility for the portion of the study performed for the sponsor. Indeed, the purpose of the requirement that the sponsor notify a grantee or subcontractor that the work being performed is a part of a nonclinical laboratory study which must be conducted in compliance with the good laboratory practice regulations is to assure that all parties submitting data are aware of their responsibilities under the regulation.

38. Several comments requested exemption for certain specialized services which are not commonly available, e.g., ototoxicity studies with diuretics. The comments stated that these specialized services would probably not be available to them if the stringent requirements of the regulations had to be met by the service organization.

The Commissioner concludes that certain specialized services cannot be exempted from these regulations. The specialized services may contribute in large measure to the agency decision to approve a research or marketing permit. If the studies are intended to provide safety data in support of an application for a research or marketing permit, their conduct falls within the scope of these regulations.

INSPECTION OF A TESTING FACILITY

39. Comments on the inspection provisions (§ 58.15) expressed concern regarding the competence and scientific qualifications of FDA investigators.

The agency has endeavored, through a specialized training program, to assure that FDA investigators are competent to perform good laboratory practice inspections. The EILP program is new, and training and evaluation will continue to improve it. The results of the pilot inspection program and the manner in which it was coducted should provide added assurance to testing facility management regarding the competence of FDA investigators. The quality of the program is not, however, dependent on the competence or training of any single individual. Inspection of findings are always subject to supervisory review within the agency, and no official action may be taken without concurrence of a number of qualified persons.

40. Several comments stated that agency inspection should be limited to those facilities under current FDA legal authority.

The scope of the regulations and the definition of a "nonclinical laboratory study" define those studies covered by the regulations. The agency intends to inspect all facilities which are conducting such studies. Many of these facilities are subject to inspection under express statutory authority vested in FDA. As noted in the preamble to the proposal (41 FR 51220):

> Inspections of many, perhaps most, testing facilities will not be conditioned upon consent. Under section 704(a) of the act, FDA may inspect establishments including consulting laboratories, in which certain drugs and devices are processed or held, and may examine research data that would be subject to reporting and inspection pursuant to section 505 (i) or (j) or 507 (d) or (g) of the act. In addition, any establishment registered under section 510(h) of the Act is subject to inspection under section 704 of the act. Thus, most manufacturing firms that conduct in-house non-clinical laboratory studies on drugs and devices, and those contract laboratories working for such firms, would be subject to FDA inspection whether or not they consented.

Facilities that are not subject to statutory inspection provisions will be asked to consent to FDA inspection. The absence of any statutory authorization does not bar FDA from asking permission to conduct an inspection, and the agency should not bar itself from seeking permission. Thus, the proposal in the comment is not accepted.

41. Several comments requested that FDA make its enforcement strategy known as promised in the preamble to the proposal.

The enforcement strategy was discussed in the preamble to the proposal (41 FR 51216) and is amplified in the compliance program which implements this regulation. The compliance program is publicly available and may be obtained by sending a written request to the agency official whose name and address appear at the beginning of this preamble as the contact for further information.

42. Two comments on § 58.15 as proposed requested that the requirement that the testing facility permit inspection by the sponsor be deleted. The comments argued that the rights and obligations of a sponsor and its laboratory are a matter of contract between them alone, and not a proper subject for government regulation.

The Commissioner has considered this issue, is persuaded that the comments are correct, and has deleted the phrase "the sponsor of a nonclinical laboratory study." At the same time, however, the Commissioner reemphasizes that, because a sponsor is responsible for the data he or she submits to the agency, the sponsor may well wish to assure that the right to inspect a testing facility is included in any contract.

43. Other comments suggested that the sponsor should accompany the FDA investigator during an inspection of a contract testing facility and that FDA access to data should require the sponsor's consent.

The Commissioner disagrees with these comments. An agency investigator may be inspecting the results of studies from several sponsors during an inspection. The logistics required to notify and arrange for several sponsors to accompany an investigator, or to obtain sponsor consent to information release, would be unworkable. FDA's practice of unannounced inspections has proved to be an effective and efficient use of scarce resources. Because of resource limitations, FDA cannot inspect each facility as often as it would like to, and the Commissioner finds that the possibility of unannounced FDA inspections at any time motivates compliance.

44. Many comments were concerned that trade secret information obtained during the inspection would be released by FDA.

The Commissioner notes that trade secrets obtained as a result of an inspection are fully protected under the provisions of section 301(j) of the act (21 U.S.C. 331(j)), as well as 18 U.S.C. 1905 and the Freedom of Information Act (5 U.S.C. 552(b)(4)) and the FDA's implementing regulations (21 CFR 20.61). Interested parties may refer to the agency's public information regulations (21 CFR Part 20), which govern agency release of documents.

45. One comment requested that the results of government laboratory inspections be made public.

The Commissioner notes that no distinctions will be made between government or nongovernment laboratories. The results of an inspection of testing facilities will be available after all required followup regulatory action has been completed.

46. The phrase "and specimens" has been added to § 58.15(a). The Commissioner finds that examination of specimens may be required to enable the agency, where necessary, to reconstruct a study from the study records.

47. Many comments stated that the inspection of records should not extend to certain records compiled by the quality assurance unit.

The Commissioner agrees and has exempted from routine inspection those records of the quality assurance unit which state findings, note problems, make recommendations, or evaluate actions taken following recommendations. These exemptions from inspection are discussed in greater detail under the discussion of § 58.35.

48. A new paragraph (b) has been added to § 58.15. This paragraph is similar to proposed § 58.200 and reiterates that a determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not relieve an applicant from any obligation under any applicable statute or regulation (e.g., 21 CFR Parts 312, 314, 514, etc.) to submit the results to FDA. If a testing facility refuses inspection of a study, FDA will refuse to consider the study in support of an application for a research or marketing permit. This refusal, however, does not relieve the sponsor from any other applicable regulatory requirement that the study be submitted.

ORGANIZATION AND PERSONNEL

PERSONNEL

49. A number of comments addressed the definition of training, education, and experience in § 58.29. Several comments considered such references too vague; several others suggested that appropriate qualifications be established by professional peer groups.

It would be inappropriate, if not impossible, for FDA to specify exactly what scientific disciplines, education, training, or expertise best suit a specific nonclinical laboratory study. These factors, which vary from study to study, are left to the discretion of responsible management and study directors. They are responsible for personnel selection and for the quality and integrity of the data these personnel will collect, analyze, document, and report. The Commissioner urges, however, that management and study directors carefully consider personnel qualifications as they relate to a particular study. The agency has uncovered instances, discussed in the preamble of the proposal (41 FR 51207), in which the conduct of a study by inadequately trained personnel resulted in invalid data. Although the Commissioner recognizes the value of certification by professional peer groups, he does not agree that the concept is appropriate for regulatory purposes.

50. Several comments said the study director should be given responsibility for assurance of qualifications of personnel.

The Commissioner agrees that, generally, the study director will be responsible for ensuring that personnel selected to conduct a nonclinical laboratory study meet necessary educational, training, and experience requirements. The Commissioner notes, however, that management also has selection and hiring responsibilities and privileges.

51. One comment stated that the requirement of § 58.29 that each individual engaged in the conduct of a study have sufficient training or experience to enable the individual to perform the assigned function should be limited to those personnel engaged in supervision and collection and analysis of data.

The Commissioner disagrees. These factors are important and should be considered for personnel other than supervisors or those engaged in collection and analysis of data. The approach suggested by the comment would ignore the fact that specific expertise is required, for example, by animal caretakers, physical science technicians, and by persons using pesticides near animal-holding areas. While the degree of education, training, and experience necessary for these positions will be quite different from the qualifications necessary for supervisors or scientific staff, the need for sufficient training or experience is no less important.

52. One comment pointed out the appropriateness of changing the term "person" to "individual" in § 58.29(a).

Because the term "person" as defined in § 58.3(h) includes partnerships, corporations, etc., the Commissioner agrees that "individual" is the proper term and has so amended § 58.29(a).

53. Seventeen comments questioned the use of, or objected to reference to, the term "curriculum vitae" for nontechnical personnel such as animal caretakers, as required in proposed § 58.29(b).

Another comment asserted that the requirement infringed on management's prerogatives without specifying how any such infringement occurred. One comment stated that the requirement that such records be retained after termination of employment was unnecessarily cumbersome.

The Commissioner does not agree that the requirement infringes on management's prerogatives. However, the Commissioner agrees with the remaining comments and has revised the section. "Curriculum vitae" has been changed to "summaries of training and experience plus job descriptions." Reference to the maintenance of records of terminated employees is deleted from this section because the requirement is redundant to the record retention requirements set forth in § 58.195(e).

54. Ten comments said the wording of § 58.29(c), relating to "sufficient numbers of personnel" and to "timely" conduct of the study, was vague.

The Commissioner purposely left the paragraph broad in context and coverage because differences in types of studies preclude any specific approach to defining numbers of personnel. The precise number of personnel reuired for a specific study, as well as for all ongoing studies, is a management decision. FDA experience, however, indicates that a shortage of qualified personnel can lead to inadequate or incomplete monitoring of a study and to delayed preparation and analysis of results, and the numbers of personnel conducting a study should be sufficient to avoid these problems.

55. Ten comments requested deletion of § 58.29(d) or clarification of the language regarding employee health habits, stating that the section was too vague and that an employer was responsible for health habits only at work. One comment submitted alternate language.

The Commissioner adopts with modifications the alternate language. The paragraph now requires only that personnel take necessary personal sanitation and health precautions to avoid contamination of test and control articles and test systems.

56. Several comments asked that the term "laboratory" in § 58.29(e), as applied to protective clothing, be deleted because it is too restrictive. Other comments suggested that the requirement that clothing be changed as often as necessary to prevent contamination be eased by changing "prevent" to "help prevent." Four related comments requested modification to reflect only "contamination affecting validity of studies."

The Commissioner agrees to the elimination of "laboratory" as applied to clothing. The provision of specialized clothing is, however, an estalished and well-known procedure for preventing contamination in a variety of situations. The Commissioner disagrees with any suggested modification of this section which weakens the intent of the regulation. The objective is to prevent contamination of the test system.

57. A number of comments addressed several aspects of § 58.29(f) regarding personal illnesses, personal health records, types of illnesses, and records of illnesses. Comments said disclosure of medical records was an invasion of privacy and of little relevance to the proper conduct of a nonclinical laboratory study.

The Commissioner agrees that documentation of personal illnesses may constitute an unwarranted invasion of privacy, and this requirement is deleted. The Commissioner disagrees with the requests for deletion of the entire paragraph, noting the relationship between personnel health and possible contamination of test systems. Revised § 58.29(f) requires individuals with illnesses that may adversely affect the quality and integrity of nonclinical laboratory studies to be excluded from direct contact with test and control articles and test systems.

The Commissioner has deleted from § 58.35(a) the sentence in question. The QAU of the testing facility is solely responsible for fulfilling the quality assurance functions for studies conducted within that facility. In those cases where portions of a study, e.g., feed analysis, are performed by a contract facility which, because it is not itself a nonclincial facility, does not have a QAU, the person letting the contract, and not the contract facility, is responsible for the performance of the quality assurance functions.

The Commissioner believes that the mechanism by which a sponsor is assured of the quality of nonclinical studies performed for it under contract is a matter that can be left to the contracting parties and need not be addressed in these regulations.

80. Three comments suggested that testing facilities be licensed or certified in lieu of having an ongoing quality assurance unit.

The Commissioner considered such an approach and rejected it before publishing the proposed regulations. (See 41 FR 51208-51209.) No persuasive arguments for changing this decision were presented in the comments. The diversity in the size and nature of nonclinical testing facilities subject to the provisions of these regulations makes licensing or certification procedures impractical. The regulation is intended to assure the quality and validity of the data obtained by each nonclinical laboratory study, and the QAU provides a mechanism to monitor each ongoing study. Licensing a testing facility could not achieve the same result.

81. Many comments objected to the provisions of § 58.35(b)(1) which require that the quality assurance unit maintain a master schedule sheet of all nonclinical laboratory studies. Some comments believed the requirement was excessive, while others questioned the proposed format and contents of the list. One comment pointed out that not every study includes all items listed.

The Commissioner is convinced that maintenance of a master schedule sheet is essential to the proper function of the Quality Assurance Unit. Only through such a mechanism can management be assured that the facilities are adequate and that there are sufficient numbers of qualified personnel available to accomplish the protocols of all nonclinical studies being conducted at a facility at any given time.

Upon careful review of the items required to be listed, the Commissioner agrees that the requirement that animal species be identified may be deleted because the requirement that "test system" be listed adequately covers this point. He has, in addition, deleted the examples of study types because he agrees that including the information is not necessary to achieve objectives of this section. The Commissioner has further reworded this section to eliminate reference to whether the final report has been approved for submission to the sponsor because the language was strictly applicable only to studies done under contract. The revised language simply requires that the status of the final report be listed.

82. Nine comments objected that § 58.35(b)(2) required too much duplicative paper.

The Commissioner has concluded that the QAU must maintain copies of study protocols to assure that they are followed and amended in accordance with the further provisions of these regulations. The Commissioner agrees that the requirement that the QAU maintain copies of all standard operating procedures would substantially increase the volume of records needed to be retained by this unit. Because there should be many copies of standard operating procedures present throughout the facility which should be freely available to QAU members, the Commissioner has deleted the requirement that these be maintained by the QAU.

83. Fifteen comments suggested that § 58.35(b)(3) be deleted on the basis that FDA should not dictate how the QAU achieves its objectives. One comment suggested that "inspect" be changed to "audit."

The Commissioner remains convinced of the need for a formal mechanism through which the QAU maintains oversight of the conduct of a study. Such a mechanism must be based on direct observation in order that the independence of the QAU be preserved. The Commissioner has retained the word "inspect" in preference to "audit." "Inspect" more accurately conveys the intent that the QAU actually examine and observe the facilities and operations for a given study while the study is in progress, whereas "audit" could be interpreted to mean simply a detailed review of the records of a study. Because the QAU function is to observe and report the state of compliance with the regulations and to determine whether the protocol is being followed rather than to verify the results of a study, "inspect" more properly conveys the agency's intent.

84. Fourteen comments addressed the need to inspect "each phase of a study * * * periodically," seeking clarification or different language. Nine of these comments called for the use of random sampling procedures in choosing studies or phases of studies to inspect in order to decrease the workload and resource requirements of the QAU.

The Commissioner does not agree that random sampling would be an adequate method of evaluation in the nonclinical laboratory setting. In situations which involve the repetition of similar or identical procedures, random sampling can provide an adequate means of quality control. Here, however, the differences among study operations and among the personnel conducting them invalidate any assumption that the conduct of one phase of one study is representative of the conduct of that phase of another or of other phases of a single study. The term "each phase" is intended to emphasize the need for repeated surveillance at different times during the conduct of a study so that each critical operation is observed at least once in the course of the study. The term "periodically" is retained to indicate the need for more than one inspection of certain repetitive continuing operations that are part of the conduct of longer term studies such as animal observations and diet preparation.

85. Many comments objected to the proposed requirement that any problems found by the QAU be brought to the attention of management and appropriate responsible scientists. Some felt that this would require that excessive resources be spent on minor problems. Others felt that notification of appropriate supervisory personnel rather than management was sufficient.

The Commissioner agrees that only those problems likely to affect the outcome of the study need to be brought to the immediate attention of personnel who are in a position to resolve those problems, and the language of § 58.35(b)(3) has been changed accordingly. The term "management" in its ordinary usage means appropriate supervisory personnel and has not, therefore, been changed.

86. More than 40 responses to proposed § 3e.33(b)(4) objected to the specific time frames required for evaluation. Several comments suggested that the paragraph be deleted. Others objected to the specific requirements, and still others stated that appropriate times for evaluatuations should be selected by management.

The Commissioner advises that periodic inspection is necessary and that the time periods specified are the minimum required to assure that a study is being conducted in compliance with the regulation. Should deviations be found during the periodic inspections, there may still be time to take corrective action. The Commissioner has, however, determined that inspection of studies lasting less than 6 months need only be conducted at intervals adequate to assure the integri-

ty of the study and that specific time intervals for such studies need not be set out in this regulation. The requirement that studies lasting more than 6 months be inspected every 3 months remains unchanged. The section has been added to § 58.35(b)(3).

87. Several comments requested that the phrase "complete evaluation" in proposed § 3e.33(b)(4) be clarified.

The Commissioner has changed the term "complete evaluation" to "inspect." The function of the QAU is to inspect studies at specified intervals to maintain records required by this regulation, and to report to management and the study director deviations from the protocol and from acceptable laboratory practice. Evaluation of any reported deviations is left to the study director and to management.

88. Fifteen comments sought deletion of § 58.35(b)(4), which requires the periodic submission of status reports to management and the study director. Three comments questioned the need to note problems and corrective action taken.

The Commissioner has retained this provision as proposed. Only through the submission of such status reports can management be assured of the continuing conformity of study conduct to the provisions of these regulations. Because § 58.35(b)(3) has been revised to require that only significant problems be reported immediately to management, the periodic status report becomes even more important as a means of informing management of minor problems and normal study progress. The status reports are needed to document problems and corrective actions taken so that management can be certain that quality is being maintained and that management intervention is not required. The timing of such reports may be determined by management.

89. Six comments objected that the term "prior" preceding "authorization" in § 58.35(b)(5) was too restrictive. The comments pointed out that unforeseen circumstances may prevent prior authorization for deviations from standard procedure and that the QAU should be concerned with the documentation of the deviation, not with whether prior authorization existed. Two comments stated that the QAU cannot assure that deviations do not occur but can determine, by inspection, whether deviations were documented.

The Commissioner is persuaded that prior authorization cannot always be obtained. For example, a fire in the facility would necessitate immediate action. The Commissioner agrees that documentation of the deviation rather than prior authorization is the important point and has deleted "prior" and added "documentation." In addition, "assure" has been changed to "determine" to respond to the comments and to reflect more accurately the Commissioner's intent. Section 58.35(b)(5) now reads: "Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation."

90. Several comments objected to the wording of § 58.35(b)(6), which states that the QAU shall review the final study report. The comments stated that such review requires a scientific judgment and is not an appropriate function for the QAU to perform. One comment suggested that the requirement should be modified to allow for random sampling rather than a complete review of all studies.

The Commissioner agrees that the QAU should not attempt to evaluate the scientific merits of the final report. Therefore, he has modified the paragraph. The QAU must however ensure that the final report was derived from data obtained in accordance with the protocol. Data in the final report significantly contributing to the quality and integrity of a nonclinical laboratory study shall be reviewed. A random sampling approach is not acceptable.

90a. The Commissioner has added to § 58.35 new paragraph (b)(7) which requires that the QAU prepare and sign a statement to be included with the final report which specifies that dates inspections of the study were made and findings reported to management and the study director. This requirement clarifies the fact that QAU review should extend through the completion of the final report and provides a mechanism for documenting that the review has been completed. A conforming section has been added to the final report requirements of § 58.185 as new paragraph (a)(14).

91. Many comments argued that requiring all portions of a quality assurance inspection to be available for FDA inspection might serve to negate their value as an effective management tool for ensuring the quality of the studies during the time in which the studies are being conducted.

The Commissioner shares the concerns of the comments that general FDA access to QAU inspection reports would tend to weaken the inspection system. He believes that FDA's review of quality assurance programs is important, and he recognizes the need to maintain a degree of confidentiality if QAU inspections are to be complete and candid. Therefore, the Commissioner has decided that, as a matter of administrative policy, FDA will not request inspections and copying of either records of findings and problems or records of corrective actions recommended and taken; and §§ 58.15 and 58.35(c) have been revised to separate those records subject to regular inspection by FDA from those records not subject to such inspection. Exempt from routine FDA inspection are records of findings and problems as well as records of corrective actions recommended and taken. All other records are available. Although the Commissioner is deleting the requirement in new § 58.35(d) that testing facility management shall, upon request by an authorized employee, certify in writing that the inspections are being performed and that recommended action is being or has been taken. Upon receiving such a request, management is required to submit the certification of compliance. A person who submits a false certification is liable to prosecution under 18 U.S.C. 1001.

The one exception to FDA's policy of not seeking access to records of findings and problems or of corrective actions recommended and taken is that FDA may seek production of these reports in litigation under applicable procedural rules, as for otherwise confidential documents.

92. Many comments objected that requiring internal quality assurance audits to be available to the agency might violate the constitutional privilege against compelled self-incrimination.

The Commissioner disagrees with the comments. It is settled that the privilege against compelled self-incrimination is an individual privilege relating to personal matters; the privilege is not available to a collective entity, such as a business enterprise, or to an individual acting in a representative capacity on behalf of a collective entity. *California Bankers Ass'n* v. *Schultz*, 416 U.S. 21, 55 (1974); *Bellis* v. *United States*, 417 U.S. 85 (1974); *United States* v. *Kordel*, 397 U.S. 1, 8 (1970); *Curcio* v. *United States*, 354 U.S. 118, 122 (1957); *United States* v. *White*, 322 U.S. 694, 699 (1944); *Wilson* v. *United States*, 221 U.S. 361, 382-384 (1911); *Hale* v. *Henkel*, 201 U.S. 43, 74-75 (1906). Even for individuals, the privilege against compelled self-incrimination is inapplicable where a reporting requirement is applied to an "essentially noncriminal and regulatory area of inquiry," where self-reporting is the only feasible means of securing the required information, and where the requirement is not applied to a "highly selective group inherently suspect of criminal activities" in an "area permeated with criminal statutes." *California* v. *Byers*, 402 U.S. 424, 430 (1971); *Marchetti* v. *United States*, 390 U.S. 39 (1968); *Albertson* v. *SACB*, 382 U.S. 70, 79 (1965); *Shapiro* v. *United States*, 335 U.S. 1 (1948).

ACCESS TO PROFESSIONAL ASSISTANCE

93. Comments on proposed § 3e.35 suggested rephrasing the statement to specify that professional assistance be authorized by the study director, that it be either in person or by telephone, that it be available within a reasonable period, and that reference to availability of a veterinary clinical pathologist be included. Other comments suggested that the concept was duplicative of the function of the study director and should be deleted.

The Commissioner proposed this requirement to assure that a scientist or other professional would be available to respond to requests for assistance or consultation from less experienced personnel. However, because management is responsible for assuring that personnel are available and that personnel clearly understand the functions they are to perform, and because the study director has overall responsibility for the technical conduct of the study, access to professional assistance is a matter best left to management's discretion. Therefore, the section is deleted from the final regulations.

FACILITIES

GENERAL

94. Many comments requested definition or clarification of the terms denoting separation (i.e., separate area, defined area, separate space, and specialized area), which are used in §§ 58.41, 58.43, 58.47, 58.49, and 58.90.

The Commissioner's intent in proposing that there be defined (and, where required, separate or specialized) areas in a testing facility was to assure the adequacy of the facility for conducting nonclinical laboratory studies. This intent is more clearly stated in the revised second sentence of § 58.41, which now reads: "It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study." The important point is that the facility be designed so that the quality and integrity of the study data is assured. The manner in which the separation is accomplished may be determined by testing facility management.

Adequate separation may be, in various situations, a function of such factors as intended use of the specific part of the facility, space, time, and controlled air. The broad variety of test systems, test and control articles, and the size and complexity of testing facilities preclude the establishment of specific criteria for each situation. For these reasons the Commissioner declines to include in the regulation either a definition or specific examples of methods for achieving adequate separation.

95. One comment suggested that a number of additional animal care and facility requirements be added to the regulations. The suggestions included, e.g., ambience to assure nonstressful conditions; ventilation and room access arranged to prevent cross contamination; and surveillance of animal health before and during a test or experiment.

The Commissioner concludes that no additional requirements need to be added because the regulation, as it stands, adequately covers the additions proposed by the comments. For example, ventilation and room access arranged to prevent cross contamination are addressed by the degree of separation requirement in § 58.41.

ANIMAL CARE FACILITIES

96. Many comments suggested that accreditation of animal care facilities by a recognized organization should provide adequate evidence that a testing facility is in compliance with § 58.43(a). One comment suggested accreditation by recognized organizations for analytical laboratories.

Although the Commissioner is aware of the value of accreditation programs, he cannot delegate FDA's responsibility for determining compliance with these regulations to an organization over which FDA has no authority. Few, if any, accreditation programs cover the same areas covered by this regulation. Furthermore, the Commissioner is unaware of any facility accreditation program which is mandatory. The agency's obligation to inspect a testing facility for overall compliance would not be altered by the fact that a facility was otherwise accredited.

97. Numerous comments objected to the requirements concerning separation of species, isolation of projects, and quarantine of animals as impractical and not necessary in all instances, e.g., separation of species in large animal studies and quarantine of all newly acquired animals. Some of the comments stated that the requirements of this section allow no latitude for judgment concerning their applicability.

The Commissioner reiterates that all requirements may not be applicable or necessary in all nonclinical laboratory studies and that the degree to which each requirement should apply in each case can be determined by informed judgment. Because of the variability of nonclinical laboratory studies, a degree of flexibility in applying the requirements of § 58.43(a) is necessary, and the language of § 58.43(a) is amended to read: "A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals." As noted in the general discussion at the beginning of this preamble, all references to other standards ("The Animal Welfare Act") have been deleted.

98. Several comments suggested that § 58.43(b) be amended to include isolaton of test systems with infectious diseases as well as isolating studies conducted with infectious or otherwise harmful test articles.

The Commissioner agrees that test systems with infectious diseases should be isolated. Proposed § 3e.49(b) provided for specialized areas for handling volatile agents and hazardous aerosols. Section 3e.49(b) also provided for special procedures for handling other biohazardous materials. Proposed § 3e.49(c) provided for special facilities or areas for handling radioactive materials.

To clarify all these requirements, the Commissioner has amended § 58.43(b) to read: "A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents." The provisions in proposed § 3e.49(b) and (c) regarding specialized areas for handling volatile agents, hazardous materials and radioactive materials are deleted from § 58.49.

99. One comment on § 58.43(c) suggested that, in addition to the area designated for the care and treatment of diseased animals, a separate area should be provided for animals with contagious diseases.

The Commissioner agrees, and the paragraph is amended to allow for an area for treatment of animals with contagious diseases, and it is to be separate from the area designated for the care and treatment of diseased animals.

100. Several comments questioned the requirement for separate areas for diseased animals, indicating that often such animals are sacrificed rather than treated.

The Commissioner does not agree that a separate area is not always needed for diseased animals. Although diseased animals may be sacrificed, this is not always the case, and it may not always be possible immediately to sacrifice diseased animals. Thus, a separate area should be available for such animals until sacrifice can be accomplished.

101. One comment requested that § 58.43(e), which deals with facility design, construction, and location to minimize disturbances that interfere with the study, should also define the

acoustic and sound-insulating requirements necessary to satisfy this requirement.

The Commissioner concludes that it is impractical to attempt to define acoustic and sound insulation requirements. It would be equally impractical to attempt to define all other types of possible disturbances that might interfere with a study.

ANIMAL SUPPLY FACILITIES

102. One comment asked that § 58.45 be clarified by specifically excluding "carriers" from the storage requirements.

The term "carrier," as used in § 58.113, is the material with which the test article is mixed, e.g., feed. The Commissioner concludes that it is necessary to provide facilities for proper storage of carriers and declines, therefore, to exclude them from the storage requirements.

103. One comment requested deletion of the section, stating that it discusses items not appropriate for FDA concern.

Improper storage of feed, carriers, bedding, supplies, and equipment can adversely affect the results of a study. Therefore, the Commissioner finds these matters to be of legitimate concern to FDA and declines to delete the section.

104. Two comments stated that separate storage space need not be required as long as material is properly stored and does not interfere with the conduct of the study.

The Commissioner agrees with these comments, in principle, but is convinced that storage areas for feed and bedding should be separate from the areas housing the test system to preclude mixups and contamination of the test systems. The section has been modified by adding the words "as needed."

FACILITIES FOR HANDLING TEST AND CONTROL ARTICLES

105. One comment stated that § 58.47, as worded, represented an impossible standard and suggested that use of the "designed to prevent" concept would be more realistic.

The Commissioner rejects this comment. The inherent purpose or "design" of all regulations is to prevent or require some action, and the use of the phrase "designed to prevent" would be an awkward and ambiguous modification of § 58.47.

106. Numerous comments objected to creating the number of separate or defined areas proposed by § 58.47, stating that the volume of testing would make it infeasible to create all the separate areas. One comment asked whether eight separate areas were required.

The Commissioner reiterates that the purpose of this section is to assure that there exists a degree of separation that will prevent any one function or activity from having an adverse effect on the study as a whole. Because of the wide variety of studies covered by these regulations, a degree of flexibility is appropriate in applying these requirements, and the degree to which each requirement should apply in each case may vary. To make this clear, the term "defined" has been deleted from § 58.47. Section 58.47(a) now reads: "As necessary to prevent contamination or mixups, there shall be separate areas for * * *." There is no specific requirement for eight separate areas.

LABORATORY OPERATION AREAS

107. A number of comments stated that § 58.49 required clarification, that in some instances more than one activity could be permitted in the same room, and that certain of the requirements would not be appropriate in every case.

The Commissioner agrees that the section as proposed was subject to misinterpretation. Because of the nature and scope of the types of studies subject to these regulations, it would be inappropriate to set specific uniform requirements for all studies. Therefore, the provisions are revised to make it clear that reasonable judgments regarding area and space requirements may be made on the basis that a particular function or activity will not adversely affect other studies in progress. Proposed § 58.49(b) has been revised, and the references to biohazardous materials has been added to the list of activities in § 58.49(a). (See the discussion at paragraph 98 above.)

108. Two comments suggested that the wording of § 58.49(a) be changed to refer to "adequate" rather than "separate" laboratory facilities, stating that animal studies require that laboratory facilities be available on the immediate premises. One comment requested that provisions be made for the use of outside laboratory facilities.

The Commissioner concludes that the term "separate" is proper in the context of § 58.49(a). He does not agree that laboratory facilities must be available on the immediate premises of the testing facility, and finds that many laboratory functions can be conducted properly in separate buildings or by independent laboratories located outside the testing facility.

109. Two comments on § 58.49(b) stated that the requirement that space and facilities separate from the housing areas for the test systems be provided for cleaning, sterilizing, and maintaining equipment and that supplies should apply only to major equipment.

The Commissioner does not agree. The objective of the requirement is to prevent the occurrence of those adverse effects which might result to a study from the activities of cleaning, sterilizing, and maintaining. No meaningful distinctions based on "major" or "not major" equipment can be made.

110. One comment on § 58.49(b) stated that the proposed wording did not have useful application in all test systems or studies and that the section should be rewritten to focus on the intended principle and not on the way to achieve it.

The section has been revised. It now reads, "separate space shall be provided for cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study." The revised wording grants flexibility in application as long as study results are not affected.

SPECIMEN AND DATA STORAGE FACILITIES

111. Several comments asked whether § 58.51 applied to completed or ongoing studies. Concern was also expressed that limiting access to storage areas to authorized personnel was not feasible.

This section is amended to apply to archive storage of all raw data and specimens from completed studies. The commissioner cannot agree, however, that limiting access of the archives to authorized personnel only is not feasible. Prudence would dictate such limited access even in the absence of a requirement. The potential for misplaced data and specimens is too great to allow unlimited access to the archives.

ADMINISTRATIVE AND PERSONNEL FACILITIES

112. One comment on § 58.53(a) stated that the section was unnecessary because adminsitrative functions had been previously defined in §§ 58.29, 58.33, and 58.35.

The Commissioner notes that this section specifies facilities rather than duties. References to OSHA regulations have been deleted.

EQUIPMENT

EQUIPMENT DESIGN

113. Five comments on § 58.61 stated that the section was fragmented and redundant.

The Commissioner agrees with these comments and has consolidated the section into one paragraph, which reads: "Automatic, mechanical or electronic equipment used in the generation, measurement or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capac-

ity to function according to the protocol and shall be suitably located for operation, inspection, cleaning and maintenance." This consolidation eliminates the fragmentation and redundancy of the proposal and specifies clearly that the requirements are limited to that equipment which, if improperly designed, or inadequately cleaned and/or maintained, could adversely affect study results.

114. Two comments objected to the undefined general terms "adequate" and "appropriate" in § 58.61.

The Commissioner points out that broad terms are necessary because of the wide range of equipment used in the studies covered. Exact design and capacity requirements for each piece of equipment are clearly beyond the scope of these regulations.

115. Four comments on § 58.61 stated that how cleaning is accomplished is irrelevant and that the regulation should emphasize accomplishment rather than ease of accomplishment.

The Commissioner agrees that the primary concern is that adequate cleaning be accomplished. However, past experience has demonstrated that when equipment is not designed and located to facilitate cleaning and maintenance, it is much less likely to be adequately cleaned and maintained.

MAINTENANCE AND CALIBRATION OF EQUIPMENT

116. Five comments suggested that § 58.63(a) should allow the required functions to be performed at the time the equipment is used rather than specifying that the functions be performed regularly.

The Commissioner agrees that performing these functions at the time of use is satisfactory and is amending § 58.63(a) to provide flexibility. The second sentence of this section now reads: "Equipment used for the generation of data shall be adequately tested, calibrated and/or standardized."

117. Two comments suggested that "calibrated" should be changed to "standardized" because the word "calibrated" normally means a performance check against known standards, whereas "standardized" normally means to make uniform.

The Commissioner finds that for some equipment the term "calibrated" is more appropriate and for other equipment the term "standardized" is more appropriate. Revised § 58.63(a) allows application of either term.

118. Two comments suggested that the reference to the use of cleaning and pest control materials is misplaced in § 58.63(a).

The Commissioner agrees that this use is more appropriately addressed under "Testing Facility Operations", and the requirements have been transferred to § 58.90(i).

119. Comments requested a precise definition of the equipment for which § 58.63(b) requires written standard operating procedures.

The Commissioner advises that because of the range of study and product types covered, such a list is impractical. The language of this section is retained as proposed to encompass the total range of equipment used in conducting nonclinical studies.

120. Eleven comments questioned the appropriateness of designating a responsible individual in § 58.63(b).

The Commissioner has changed "individual" to "person" as defined in § 58.3(h) to allow for designation of an organizational unit.

121. One comment indicated the need for a clear FDA policy regarding primary calibration standards.

The Commissioner concludes that proper standards are the responsibility of management, and these are to be set forth in the standard operating procedures.

122. One comment agreed with the standard operating procedure requirements of § 58.63(b), but suggested a several year phase-in period.

The Commissioner concludes that 180 days is a sufficient time period for developing standard operating procedures. Furthermore, the Commissioner's intent to require such procedures has been known since November 1976, when the proposed regulation was published.

123. Seven comments suggested that the manufacturer's recommendations should be sufficient for standard operating procedures. Additionally, one comment pointed out that maintenance could be subcontracted and a certificate should be allowed.

The Commissioner advises that the regulation does not preclude the use of manufacturer's recommendations as part of the standard operating procedures, nor does it preclude subcontracting maintenance. The Commissioner advises, however, that if a facility decides to subcontract maintenance, that fact does not relieve the facility of the responsibility for maintenance.

124. One comment argued that the requirement that all equipment records specify remedial action to be taken is excessive, and two comments said there are too many variables to specify in advance the remedial action to be taken.

The Commissioner notes that trouble-shooting charts are available for most equipment. The remedial action taken may influence the results of the study and therefore must be documented.

125. Several comments suggested that the equipment for which standard operating procedures are required be limited by rewording in one of the following ways: "major" equipment, "equipment used in data collection," or "delicate, complex equipment."

The Commissioner has considered the comments and has modified the language of § 58.63(b) to require that standard operating procedures describe in "sufficient" detail the procedures to be used in cleaning, testing, and standardizing equipment. The Commissioner points out that § 58.81(a) (standard operating procedures) states that the written standard operating procedures are to be those which management is satisfied are adequate to ensure the quality and integrity of study data. While the Commissioner does not find it feasible to confine the requirement for standard operating procedures to "major" equipment, he does find that the regulation clearly contemplates that the required procedures need be only as detailed as deemed necessary to assure the integrity of the study data. Simple equipment, therefore, should require only brief standard operating procedures.

126. Five comments suggested that written records for nonroutine repairs should only be required where the nature of the malfunction could affect the validity and integrity of the data.

The Commissioner rejects this suggestion because it is not always possible to make this judgment ahead of time.

127. Many comments argued that the recordkeeping requirements of § 58.63(c) are excessive.

The Commissioner has concluded that the cost of maintaining records of cleaning exceeds the benefits, and this requirement is deleted. However, the requirement for maintaining records of all inspections, maintenance, testing, calibrating and/or standardizing operations is retained because these records may be necessary to reconstruct a study and to assure the validity and integrity of the data.

128. One comment proposed that a new sentence, reading as follows, be added to § 58.63(c): "Where appropriate, the written record noted above may consist of a notation temporarily fastened to the piece of equipment stating when the last specified action with respect to the equipment was taken."

The Commissioner finds that the suggested approach is not precluded by the language of the section as written, but cautions that where such an approach is used, the notations constitute records which must be retained as required by § 58.195(f).

129. One comment asked whether each client of a contract facility must receive a copy of the equipment maintenance and calibration records.

The Commissioner concludes that the regulation does not so require.

TESTING FACILITIES OPERATION

STANDARD OPERATING PROCEDURES

130. Two comments suggested deleting § 58.81 in whole or in part. Several others said the requirements for standard operating procedures were unnecessary and burdensome.

The Commissioner does not agree. The use of standard operating procedures is necessary to ensure that all personnel associated with a nonclinical laboratory study will be familiar with and use the same procedures. These requirements will prevent the introduction of systematic error in the generation, collection, and reporting of data, and they will ensure the quality and integrity of test data that are submitted to FDA to become the basis for decisions made by the agency. The Commissioner recognizes that the requirements for standard operating procedures may place an additional burden on testing facilities, but finds that the resulting benefits should outweigh the burden. The requirements will benefit the public by producing better quality data and will benefit the testing facility by reducing the need to repeat nonclinical laboratory studies because of errors in the data.

131. A few comments suggested that responsibility for the standard operating procedures should be specified.

The Commissioner has concluded that this function should reside with the management of a facility, and the first sentence of § 58.81(a) is revised accordingly.

132. Several comments suggested that the responsibility for authorizing significant changes in established procedures be vested in someone other than management.

The Commissioner disagrees. Because standard operating procedure will often apply to more than one study in a testing facility, the Commissioner believes that significant changes to a standard operating procedure, which could affect several different studies, should be authorized by management.

133. Several comments stated that standard operating procedures should not apply to certain types of test systems, that the requirement would introduce difficulties in open-ended exploratory experimentation and electromedical equipment testing, that the approach would not lend itself to rapidly changing methodology such as mutagenicity testing, and that requiring chemical standard operating procedures for each test and procedure was not realistic.

The Commissioner agrees that routine standard operating procedures should not apply to exploratory studies involving basic research. He does not agree, however, that electromedical equipment testing should be exempt unless such testing does not fall under the definition of "nonclinical laboratory study." Standard operating procedures are feasible for studies using methods which change rapidly and for studies using any test system. In the case of chemical procedures, the Commissioner finds that it is realistic to require written standard operating procedures for each test.

134. One comment recommended that the phrase "written standard operating procedures" in § 58.81(a) be changed to "documented appropriate operating procedures." The same comment suggested that the term "ensure" in the first sentence of § 58.81(a) be changed to "maintain."

The Commissioner disagrees with both suggestions. The term "standard operating procedures" refers to routine and repetitive laboratory operations. "Appropriate operating procedures," as a phrase, implies that such procedures could be changed at will. The Commissioner also rejects the suggestion that "ensure" be changed to "maintain." The purpose of written standard operating procedures is to ensure the quality and integrity of the data generated in the course of nonclinical laboratory study. The term "maintain" assumes the procedures already in existence are sufficient to ensure the quality and integrity of the data when, in fact, they may not be sufficient.

135. One comment said that the term "adequate" in the first sentence of § 58.81(a) is a nonprecise term.

The Commissioner agrees, but finds that a testing facility may have a broad range of divergent standard operating procedures for many different studies and that it is impractical to define the adequacy of such procedures for all types of tests. A determination of the adequacy of each standard operating procedure is the responsibility of the management of the testing facility.

136. Numerous comments asked what changes or deviations from standard operating procedures should be documented in the raw data, as required in § 58.81(a). One comment said any deviation should be documented, whether authorized or not.

Every deviation or change in a standard operating procedure should be documented in the raw data. The second sentence of § 58.81(a) has been revised for clarity. It now reads: "All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data."

137. Seven comments indicated that it is inappropriate to require that every minor deviation be documented and reported in writing to the QAU.

The Commissioner agrees that, because the QAU is no longer required to maintain copies of standard operating procedures, it is inappropriate to require that every deviation be reported in writing to the QAU. It is sufficient that all deviations from standard operating procedures be authorized by the study director and documented in the raw data. No exceptions can be made for "minor" deviations. Because any deviation or change may affect the outcome of a study, it is not possible to judge in advance whether or not a deviation is, in fact, "minor."

138. Several comments indicated that the requirement for standard operating procedures should be general in nature.

The Commissioner disagrees. In the proposal, the Commissioner cited evidence from agency investigations of certain testing facilities that had failed to maintain written standard operating procedures of the kind outlined in § 58.81(b). As a result, certain technical personnel were unaware of the proper procedures required, e.g., for care and housing of animals, administration of test and control articles, laboratory tests, necropsy and histopathology, and handling of data. The Commissioner has concluded that a specific delineation of standard operating procedures will allow for uniform performance of testing procedures by personnel and consequent improvement in the quality of the data.

139. Two comments indicated that the requirements for standard operating procedures set out in § 58.81(b) (1) through (12) largely concern animal studies and that this should be so indicated in this section.

The Commissioner agrees that many of the provisions listed in § 58.81(b) are applicable only to studies involving animals. Such is true, however, of many provisions throughout the regulations, and no special mention of the fact is required here. The Commissioner emphasizes that operations requiring standard operating procedures are not limited to those listed in § 58.81(b).

140. One comment suggested that the phrase "and control" be deleted from the first sentence of § 58.81(b)(3), which requires standard operating procedures for test and control articles, because a control article may often be a competitor's product.

The Commissioner does not agree. Where a control article is a commercially available product, its specifications and characterization may be documented by its labeling.

141. Several comments suggested that the last sentence of proposed § 58.81(b)(3), which reads: "The testing program shall be designed to establish the identity, strength, and purity of

the test and control substances, to assess stability characteristics, where possible, and to establish storage conditions and expiration dates, where appropriate" be deleted or suggested that the sentence be transferred to another section.

The Commissioner agrees. The sentence is deleted from § 58.81(b)(3), and appropriate portions of the sentence are transferred to § 58.105(a). The concepts expressed in this sentence properly belong in the section of the regulations relating to "Test and Control Article Characterization." The phrase "testing and administration" has been deleted from the first sentence of § 58.81(b)(3) for the same reason. To specify clearly the Commissioner's intent, "method of" has been added to § 58.81(b)(3) to modify "sampling." Revised § 58.81(b)(3) now reads: "Receipt, identification, storage, handling, mixing and method of sampling of the test and control articles."

142. One comment stated that § 58.81(b)(9), "Histopathology," and § 58.81(b)(8), "Preparation of specimens," were duplicative.

The Commissioner has revised § 58.81(b)(8) to read: "Collection and identification of specimens" to distinguish the requirement from § 58.81(b)(9), "Histopathology." The term "histopathology" covers the examination of specimens, not their collection and identification.

143. Eight comments recommended a rewording of the requirement in proposed § 3e.81(b)(12) that standard operating procedures be established for the preparation and validation of the final study report.

The Commissioner concludes that the requirement should be deleted because the reporting provisions of § 58.185 adequately describe the requirements for final reports. A new paragraph, § 58.81(b)(11), covering "maintenance and calibration of equipment," has been added to reflect the requirements of § 58.63(b).

144. Seven comments suggested that in § 58.81(c) the requirement that standard operating procedures be available at all times to personnel in the immediate bench area be broadened to be within "easy access." Another comment said the location of such materials should be left to the facility's discretion.

The Commissioner has concluded that unless standard operating procedures are immediately available within the laboratory area they are not within "easy access" and may not be consulted by personnel when routine operations are being performed. The first sentence in § 58.81(c) has been edited for clarity, but the requirement remains.

145. Several comments were received regarding § 58.81(c) and the use of textbooks as standard operating procedures. One comment suggested that textbooks be considered appropriate as part of a standard operating procedure. Two comments assumed that standard operating procedures would permit the incorporation of textbooks by reference. One comment suggested that supplementary material should be written to augment textbooks. An additional comment suggested that textbooks be used in the absence of standard operation procedures.

Standard operating procedures should be set forth in writing, and textbooks may be used as supplements to written standard operating procedures. Reference to applicable procedures in scientific or manufacturer's literature may be used as a supplement to written standard operating procedures. For example, a standard operating procedure could refer to the pertinent pages of any portion(s) of a textbook or other published literature that might be pertinent to a laboratory procedure performed; these supplementary materials need not be incorporated verbatim in the standard operating procedure, but would be required to be immediately available in the laboratory area for the use of personnel. The last sentence of § 58.81(c) is revised to make this point clear. Additionally, § 58.81(d) regarding a historical file of standard operating procedures has been clarified to read: "A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained."

REAGENTS AND SOLUTIONS

146. Numerous comments on § 58.83 said that to require that the labeling of reagents and solutions in laboratory areas include the method of preparation was neither feasible nor necessary.

The Commissioner agrees and is deleting the phrase "method of preparation" from § 58.83 because the method of preparation could be too lengthy to fit readily on the label. The method of preparation of reagents and solutions should, however, be addressed by the standard operating procedures.

147. Several comments stated that the provision for the handling and use of deteriorated materials and materials of substandard quality should specify only that they not be used and should not specify or require their removal from the laboratory because their removal should be left to the discretion of the laboratory.

The Commissioner agrees, and § 58.83 has been revised accordingly.

148. One comment suggested that the phrase "used in nonclinical studies" be substituted for the phrase "in the laboratory areas" in the first sentence of § 58.83.

The Commissioner disagrees with this comment. All reagents and solutions used in a laboratory conducting a nonclinical study should be properly labeled as provided in the regulation to preclude inadvertent mixups of reagents and solutions that are used in such studies with those that are not intended for such use.

149. Two comments suggested that the phrase "Deteriorated materials and materials of substandard quality" in the second sentence of the section be changed to incorporate the terms "reagents" and "solutions."

The Commissioner agrees and is revising the second sentence of § 58.83 accordingly. Revised § 58.83 now reads: "All reagents and solutions in laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used."

ANIMAL CARE

150. Several comments raised the issues of unnecessary animal experimentation and the humane care of animals.

The issue of using animals in laboratory experiments designed to establish the safety of regulated products has been raised many times in the course of agency rulemaking. The position of FDA has been consistent on this issue. The use of animal tests to establish the safety of FDA-regulated products is necessary to minimize the risks from use of such products by humans. The humane care of test animals is a recognized and accepted scientific and ethical responsibility and is encouraged both by various agency guidelines and the Animal Welfare Act. The good laboratory practice regulations should, in fact, encourage the humane treatment of animals used in nonclinical laboratory studies by establishing minimum requirements for the husbandry of animals during the conduct of such studies. In addition, there should occur a reduction in the amount of animal testing that has to be repeated or supplemented because the original studies were inadequate or inappropriate to establish the safety of FDA-regulated products.

151. Numerous comments objected to the incorporation by reference of guidelines and standards proposed in § 58.90(a).

As noted early in the preamble, all references to other standards such as the Animal Welfare Act of 1970 and HEW Publication No. (NIH) 74-23 have been deleted. Section 58.90(a) is revised to read: "There shall be standard operating procedures for the housing, feeding, handling and care of animals."

152. Several comments stated that the quarantine of animals required in

§ 58.90(b) was impossible in some cases, unnecessary under certain conditions, and would prevent the use of certain animals, such as "timed-pregnant" mice. Other comments said the paragraph could be interpreted to require a separate quarantine area or an extensive quarantine time period.

The purpose of this paragraph is to require that the health status of newly received animals be known before they are used. This requires a separate quarantine area where necessary to determine animal health status. The concept of "separate areas" has been previously discussed. In some cases, depending on such factors as the species or type (e.g., time-pregnant) of animal, or the source and the nature of the expected use of the animal, a health evaluation can be made immediately, or soon after arrival, resulting in a very short quarantine period. The regulation does not preclude this type of health evaluation if it is done in accordance with acceptable veterinary medical practice.

153. Several comments stated that quarantine is unnecessary when animals are obtained from reputable or specific pathogen-free sources.

A health evaluation is required of all newly received animals regardless of the supply source, although the source can be a factor in determining the degree or depth of health evaluation required. Seldom can the conditions under which animals are transported from their source be considered certain to preclude the possibility of exposure of the animals to disease.

154. Some comments requested deletion of § 58.90(b) because it duplicates the animal care requirements regulations.

The Commissioner rejects these comments. The agency is responsible for animal care procedures as they pertain to testing facilities conducting nonclinical laboratory studies, and the provisions are appropriately included in § 58.90(b).

155. Several comments said that the requirements of § 58.90(c) and (d) concerning the isolation of known or suspected diseased animals and keeping animals free of disease or conditions that would interfere with the conduct of the study were impractical.

For clarity, these paragraphs are revised and combined in § 58.90(c). This paragraph deals only with those diseases and conditions that might interfere with the study. This excludes a wide range of diseases and conditions and allows the consideration of such factors as etiology and whether the disease is communicable. The section does not require isolation of all animals in a shipment from a study when only one or some of the animals are diseased, and it covers only those animals that are known or suspected to be diseased.

156. Some comments suggested that specific requirements be provided for the management of diseased animals, and one comment said the veterinary staff should be able to treat diseased animals as they deem proper.

The Commissioner concludes that it is beyond the scope and purpose of these regulations to describe detailed requirements concerning the management of diseased animals and that § 58.90(c) is sufficiently explicit to exclude the use of diseased animals that would interfere with the purpose or conduct of a nonclinical laboratory study. The regulation does not prohibit the treatment of diseased animals if such treatment does not interfere with the study. If treatment will interfere with the study, the diseased animals shall be removed from the study.

157. More than 60 comments objected to or requested revision of proposed § 3e.90(e), which called for the unique identification of all animals used in nonclinical laboratory studies. Fifty-four of the comments addressed specific issues related to this concept, e.g., unique identification of mice, costs of such systems, application to suckling rodents, injury to animals from identification systems, effects of dyes or tattoos, a lack of need in single-dose or short-term experiments, and cage identification instead of animal identification with precautions being taken to prevent animal mixups.

In the absence of a proven and acceptable method of unique identification for small rodents, the Commissioner is revising § 58.90(d) to require appropriate identification for warm-blooded animals, excluding suckling rodents, which require manipulations and observations over extended periods of time. Suckling rodents have been excluded from the requirements because of potential cannibalization by the mother. The same information needed to specifically identify each animal is required on the outside of housing containers or cages. Such identification should substantially reduce the possibility for animal mixup. Because of the varied nature of the tests conducted and the test systems used, the manner of identification is left to the discretion of the testing facility.

The Commissioner advises that whenever a study requires that animals be removed from and returned to their home cages, there is a potential for mixup. Thus, if a single-dose or short-term study requires such manipulations, the animals shall receive appropriate identification.

Because the requirement for unique identification has been deleted, the concerns expressed regarding cost, injury to the animals from various identification systems, and the effects of dyes or tattoos are no longer germane.

158. Two comments questioned whether the study director could in practice assure unique identification as proposed in § 3e.90(e), without direct observation.

The requirement has been deleted, along with the requirement for unique identification.

159. Two comments requested deletion of the last sentence of proposed § 3e.90(e) regarding the identification of specimens.

The Commissioner concludes that proper specimen identification is an integral part of proper study conduct, but that the requirement more properly belongs under standard operating procedures. Consequently, § 58.81(b)(8) now incorporates this provision.

160. One comment inquired whether, in the event animals of the same species in different tests were in the same room, FDA would require identification of all compounds. This, it was felt, would raise confidentiality questions for a contract testing facility.

The Commissioner advises that the use of coding to identify test or control articles is not precluded by § 58.90(e). The concluding phrase, "to avoid any intermixing of test animals," was deleted as redundant.

161. Proposed § 3e.90(g) required comparison of cage and animal identification for each transfer, procedures for verification, and written permission of the study director for location transfer. Seventeen comments objected to part or all of these requirements as vague, burdensome, unnecessary, and redundant.

The Commissioner agrees, and the paragraph is deleted. Procedures for the transfer and proper placement of animals are required as standard operating procedures in § 58.81(b)(12).

162. Several comments claimed that the requirements of proposed § 3e.90(h), redesignated § 58.90(f), were redundant in view of the requirement for standard operating procedures in § 58.81. Other comments stated that the incorporation of guidelines by reference was inappropriate.

The Commissioner concludes that the requirement that animal cages, racks, and accessory equipment be cleaned is appropriately included in this section even though there is some overlap with the language of § 58.81, standard operating procedures. The reference to other agency guidelines has been deleted.

163. Three comments asserted that sanitization should not always be done, because it could in certain cases interfere with the conduct of the study.

The Commissioner agrees and points out that the language in redesignated

§ 58.90(f) permits cleaning and sanitization at appropriate intervals. The section now reads: "Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals."

164. Many comments objected to proposed § 3e.90(i), redesignated § 58.90(g), which requires periodic analysis of feed and drinking water for "known interfering contaminants." Certain of these comments requested clarification or deletion, or expressed concern about the costs involved. Others argued that the use of positive and negative controls would accomplish the intent of the requirement, or that certificates of analysis from local water supply authorities and feed manufacturers should be permissible. Finally, a few comments said analysis of feed and water should only be required when there is reason to believe that a particular contaminant may have an effect on the study, and comments said the analysis requirements should be specified in the protocol.

Most of the objections raised against the analytical requirements of the section were based on misinterpretation of such requirements. The intent of the Commissioner was to require analysis for contaminants known to be capable of interfering with the nonclinical laboratory study and reasonably expected to be present in the feed or water, and not to require analysis of feed and water for all contaminants known to exist. Certain contaminants could affect study outcome by masking the effects of the test article, as was observed in recent toxicological studies of pentachlorophenol and diethylstilbestrol, in which the feeds used as carriers for the test articles were found to contain varying quantities of pentachlorophenol and estrogenic activity, respectively, that invalidated these studies by producing erratic results. The use of positive and negative controls in these examples was insufficient to compensate for the variability in contaminant content. Therefore, the Commissioner agrees with the comments that suggested that analysis of feed and water only be done when there is reason to believe that a particular contaminant may have an effect on the study, and may be present in the feed or water, and the language of both redesignated § 58.90(g) and § 58.120(a)(9) have been revised to make this clear. This clarification of the regulations should allay the concerns of those comments relating to certificates of analysis, costs, and precise definition of impurities. Acceptable contaminant limits must be specified by the protocol (§ 58.120(a)(9)), and should be determined at the time the protocol is developed, taking into account the scientific literature, the availability of suitable analytical methodology, and the practicability of controlling the level of the contaminant.

165. One comment suggested additional requirements for, e.g., analysis of nutrients and reserve samples of feed at the testing facility.

Nutrient analysis should be addressed by the facility's standard operating procedures. Requirements for reserve samples of test or control articles/carrier mixture (e.g., feed) are set forth in § 58.113(b). The Commissioner concludes that minimum requirements for those items are set forth in the regulation. The regulation does not preclude the setting of additional requirements by the sponsor and/or the testing facility.

166. Proposed § 3e.90(j) would have required feed to bear an expiration date. Twenty-three comments argued that this requirement is of dubious value, is beyond the current state of the art because of varied storage conditions, and that commercially available feed is not expiration dated, making the requirement impractical or impossible.

The Commissioner agrees with these comments, and this requirement is deleted.

167. Several comments argued that the requirement for weekly changes of bedding should be deleted. The comments stated that, in certain cases, weekly bedding changes are contraindicated.

The Commissioner agrees, and the phrase "at least once per week" is removed from § 58.90(h), which now reads, "Bedding * * * shall be changed as often as necessary to keep the animals dry and clean."

Test and Control Articles

Test and control article characterization

168. One comment suggested that § 58.105 be deleted; another suggested that the entire subpart be condensed; and three comments suggested that the section is not generally applicable to nonclinical device studies, particularly with reference to such terms as "identity, strength, quality, and purity."

The Commissioner does not agree that the section should be deleted. Its purpose is to assure that the article being tested has been thoroughly characterized or defined and that either the sponsor or the testing facility has a thorough understanding of what is being tested. The Commissioner agrees that the subpart should be condensed and has shortened it. Section 58.105(a) is modified by the inclusion of the sentence "the identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article." This addition provides for characterization of various products, including devices in terms suited to their identity or uniqueness.

169. One comment argued that the requirement that "other substances contained in the test and control substances" be accounted for, as proposed in § 58.105(a), was vague.

By this provision the Commissioner intended to indicate the need to identify and characterize solvents, excipients, inert ingredients and/or impurities that might be part of the test substance. Because these materials are included by definition in the term "test article," the Commissioner has determined that the original language was unnecessary and has deleted it.

170. Three comments sought definition of the word "batch" as used in § 58.105(a).

The term "batch" is now defined in § 58.3(n).

171. Seventeen comments on § 58.105(a) stated that because some control or reference articles might be a competitor's or a supplier's product, the assay and method of synthesis might not be available or might be confidential.

The Commissioner concludes that, in those cases where a competitor's or supplier's product is used as a control article, such products will be characterized by the labeling and no further characterization is necessary.

172. One comment stated that the testing facility should not be responsible for identity, strength, quality and purity and that this responsibility should rest with the sponsor. This comment also suggested that the requirement, as written, would inhibit the conduct of blind studies.

The Commissioner concludes that it is the responsibility of testing facility management to assure that the requisite tests have been done, either by the sponsor or by the test facility (see § 58.31(d)). In those cases where a testing facility is unable to perform the characterization test or is performing blind studies, the sponsor should perform the required testing and notify testing facility management that the characterization of the test or control article has been performed. The section, as revised, does not inhibit the conduct of blind studies: it does not require that the sponsor give the characterizing information to the testing facility, only that the sponsor notify the testing facility that the required characterization has been done.

173. One comment suggested that the requirements of § 58.105 should only apply if the integrity of the study is threatened, and another suggested that any contaminants in a test or control article should be evaluated only with respect to their impact on study validity.

The Commissioner does not agree that the requirement should be so limited. Thorough characterization of the article under test is essential because the results of the test may be compromised by possible contamination. Only by knowing the identity and quantity of the components can one predict their effect on the study. The evaluation of the impact of test and control article contaminants on the validity of the study is an important part of the thorough characterization of the test and control articles.

174. Thirteen comments suggested that characterization of the test article be permitted during the study, after its completion, or left to such time as specified in the protocol.

The Commissioner concludes that characterization of the test or control article should be determined before the initiation of the study in order to provide a means of controlling variations from batch to batch as well as to make certain that the test article meets the specifications of the protocol. As previously stated, a thorough understanding of the nature of the test article is a basic requirement for assuring the absence of contaminants that may interfere with the outcome of the study. When the stability of the test and control articles has not been determined before initiation of the study, the regulation requires periodic reanalysis of each batch of test and control articles as often as necessary while the study is in progress.

175. One comment stated that the phrase "verifying documentation" in § 58.105(a) was not clear.

The Commissioner has determined that the phrase is not needed, and § 58.105(a) is revised to delete it.

176. Seven comments suggested that stability studies required by § 58.105(b) may not always be necessary; three comments suggested that common vehicles and placebo controls, such as water, should be omitted from stability studies.

Some degree of instability may be associated with every test article that might be the subject of nonclinical laboratory study. The Commissioner concludes, therefore, that stability information must be included as part of the information upon which the agency bases a decision regarding the safety of the article. If the stability of common vehicles is generally recognized and can be documented, stability testing is not required.

177. Twelve comments suggested that the term "production" in proposed § 3e.105(c) should be deleted or changed by substitution of other terms such as "approved" or "released," stating that the use of the word was confusing. Several other comments stated that the requirement that test and control substances be derived from the smallest number of production batches consistent with their stability was not always possible or necessary.

The Commissioner agrees that the section was confusing and finds that the requirement is adequately covered by § 58.105(a). The word "batch" has been defined in § 58.3(n), and proposed § 3e.105(c) has been deleted.

178. One comment suggested that the test and control articles should be derived from a large number of batches to increase the probability that test and control articles are representative.

The Commissioner agrees that, in some cases, combining representative samples of test or control articles from various production sources or lots to form a batch may be desirable. Where this is done, however, the resulting batch, rather than the individual samples, must be characterized in accordance with § 58.105(a).

179. Eight comments on § 58.105(d) suggested that the requirement for reserve sample retention be restricted to those substances whose stability had not been previously determined. Another comment suggested that the section seems to require that a reserve sample of water be retained if water is used as the control article, and another comment suggested that the retention of a reserve sample should be left to the discretion of the sponsor.

The Commissioner does not agree that the decision to retain a reserve sample should be at the discretion of the sponsor. Maintaining a reserve sample is necessary to provide independent assurance that the test system was exposed to the test article as specified in the protocol. Reserve samples need not be reanalyzed routinely if the stability of the test or control article is well established. If, however, the results of a study raise questions as to the composition of the test or control article, retention of reserve samples allows resolution of the question. Retention of a reserve sample of water is required when it serves as the control article in a nonclinical laboratory study.

180. Eight comments on § 58.105(d) suggested that containers should be comparable rather than identical to maintain approximate ratio of mass of article to container volume.

Reserve samples should be stored in containers and under conditions that maximize their useful life. The specifications for containers are deleted from § 58.105(d), however, and are now left to the discretion of the study director.

181. Six comments said § 58.105(d) duplicated §§ 58.105(b) and 58.113(a)(2); three said that the requirement that the reserve sample be analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date may result in unnecessary testing. One comment suggested that a portion of the remaining article should be tested rather than testing the reserve sample.

The Commissioner agrees that the requirement for routine reanalysis of all test or control articles is unnecessary where stability characteristics have been well established, and this requirement has been deleted. The Commissioner does not agree that the cited sections duplicate one another. Section § 58.105(b) concerns the stability of test and control articles in a carrier mixture. But § 58.105(d) concerns reserve samples of test and control articles.

182. A number of comments on proposed § 3e.105(f) sought clarification of the requirements, definition of the term "quarantine," and deletion of the requirement to reanalyze batches returned from distribution.

The Commissioner has examined the provision as proposed and has found that the intent is achieved by the provisions of § 58.107 (test and control article handling). Proposed § 3e.105(f) has, therefore, been deleted.

TEST AND CONTROL ARTICLE HANDLING

183. One comment asserted that § 58.105 covered the specifics for handling test and control substances and that § 58.107 should be deleted.

The Commissioner disagrees with the assertion that § 58.107 repeats § 58.105. The provisions of § 58.105 apply to the characterization of test and control articles and their storage prior to use. Section 58.107 sets forth provisions for the handling and distribution of test and control articles during the course of a nonclinical laboratory study. The purpose of this section is to provide further mechanisms to assure that test and control articles meet protocol specifications throughout the course of the study, and that test article accountability is maintained.

184. Other comments argued that the language of § 58.107 should be modified and that, as written, the section was impractical.

The Commissioner does not agree that the requirements are impractical. The section has, however, been edited for clarity. Section 58.107(a) now reads, "There is proper storage." Because contamination is only one of the consequences that may result from improper handling during distribution, the Commissioner has revised § 58.107(b) to read: "Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage."

MIXTURES OF ARTICLES WITH CARRIERS

185. Many comments stated that the requirements of § 58.113 should only apply to certain types of studies, such as long term feeding studies, or should apply only in cases where problems of instability might result from mixing the test article with a carrier.

The Commissioner does not agree. The need to know that the test system is being exposed to the amounts and types of test and control articles that are specified in the protocol is common to all types of studies. The effect of mixing on the concentration and stability of the test or control article in the mixture cannot be predicted beforehand.

186. Six comments stated that the requirement that each batch of a test or control article that is mixed with a carrier be tested for uniformity of mix, stability, and release, as proposed in § 58.113, was excessive.

The Commissioner has reviewed the reasons advanced by the comments and has deleted the "for each batch" requirement. Once the uniformity of the mixture has been established for a given set of mixing conditions, it is not necessary to establish the uniformity of each subsequent batch that is mixed according to the same specifications. Similar considerations apply to stability testing. Section 58.113(a)(1) introductory text and (a) now read: "For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted: (1) to determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture." The sentence, "[I]f the nonclinical study is to be performed as a blind study, enough individual samples of the mixture shall be returned to the sponsor for analysis," has been deleted. The requirement for analysis of test or control article mixtures is adequately addressed by the revised language of § 58.113(a)(1). The mechanism of satisfying the requirement is left to the testing facility. Blind studies are discussed in paragraph 172 above.

187. One comment stated that the possibility of administration by other than the oral route should be considered.

The Commissioner agrees, and reference to the route of administration is removed.

188. Several comments said the acute and subacute toxicity studies are often conducted before there is extensive knowlege about a drug's stability and that in such cases the drug might be prepared daily. In addition, it was suggested that § 58.113(a)(2) allow for concurrent stability studies.

The Commissioner agrees with the comment and has revised the regulation to allow concurrent studies of stability to proceed with the ongoing nonclinical laboratory study.

189. Three comments on § 58.113 suggested that establishing expiration dates for a substance used up in a week seemed too stringent. Many comments suggested that the expiration dating requirement be eliminated entirely because batch sizes are established so that they will be used up prior to deterioration of the test article.

The Commissioner has considered the comments and has revised, as noted above, the requirement for labeling each batch of test or control article carrier mixture to permit concurrent stability testing. The Commissioner declines to eliminate entirely the requirement for listing of expiration dates. Expiration dates should be used, when known, to minimize the possibility that subpotent, unstable, or decomposed test or control article carrier mixtures will be used. New § 58.113(c) requires that, where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

190. Many comments on proposed § 3e.113(a)(3) stated that the requirement for tests to determine the release of the test or control substance from the carrier needed to be clarified, might be impossible to do, and were not always necessary.

The Commissioner has reviewed the comments and the section and finds that such testing should be adequately addressed by the protocol. He has, therefore, deleted the section.

191. Eleven comments suggested that the requirement that reserve samples of each batch of test or control article-carrier mixture be retained was excessive and impractical.

The Commissioner does not agree. Maintenance of reserve samples of these mixtures is necessary for the same reasons that reserve samples of test and control articles themselves are necessary. These reasons are stated in paragraph 179 above.

192. Proposed § 3e.115 incorporated principles set forth in other regulations and has, accordingly, been deleted. (See the discussion in paragraph 3.)

PROTOCOL FOR AND CONDUCT OF A NONCLINICAL LABORATORY STUDY

PROTOCOL

193. Several comments said the protocol requirements of § 58.102(a) were not relevant to specific test articles, e.g., electronic diagnostic instrumentation. Other comments objected to requiring a protocol for short-term studies or for routine tests described elsewhere in 21 CFR Chapter I. Additional comments proposed that specific requirements be imposed only where applicable, and one comment said the protocol should focus on what is intended rather than on how the intended result is to be achieved.

The Commissioner has previously discussed the types of tests and the conditions within the scope of Part 58. Because of the broad range of studies covered, specific sections may not apply to all studies. However, the Commissioner declines to exempt short-term studies or routine tests from these requirements. Any study which qualifies as a nonclinical laboratory study is subject to the requirements. The good laboratory practice regulations are both process-oriented and product-oriented, and are designed to ensure, insofar as possible, the quality and integrity of nonclinical laboratory data submitted to FDA in support of regulated products. The Commissioner recognizes that some of the requirements of this section have often not been traditionally included in a protocol. He has nonetheless concluded that the requirements are essential to ensure that all operations needed to fulfill the objectives of a study are performed and that the complete list of information required by this section is necessary to ensure that deviations, should they occur, are readily appparent.

194. One comment asked what was meant by "all methods" in § 58.120; one suggested deletion of the word "approved" to describe the protocol; and another suggested that reference to statistical methods in § 58.120(a) be deleted and that a new paragraph on statistical methods be added to the list of information required.

"All methods" refers to all operations necessary to achieve the objectives of the study, e.g., analytical methods, randomization procedures, etc. If such methods are from published sources, citation of the source would fulfill this requirement. If the methods are not from published sources, full descriptions would need to be included in the protocol. The word "approved" is retained to emphasize that a sponsor or testing facility should have a mechanism for evaluation and approval of initial protocols and all amendments. A new paragraph (a)(16) is provided to emphasize the need to consider statistical methodology in preparing a protocol.

195. Ten comments objected to the inclusion, in proposed § 3e.120(a)(3), of stability methodology as a protocol requirement because such methodology may not have been developed before the study was begun. Another comment suggested deletion of this requirement as not relevant to a proto-

col, while three comments suggested revision.

The Commissioner recognizes that stability data may not be available when a study is initiated, and this requirement is deleted from the section. The Commissioner emphasizes, however, that determination of the stability of the test and control articles is a responsibility of the study director, that determination of the stability of the articles per se is required under § 58.105(b), and that determination of the stability of the article/carrier mixes is required under § 58.113.

196. Numerous comments on proposed § 3e.120(a)(4) objected to the listing of the names of laboratory assistants and animal care personnel in the protocol because these jobs are subject to constant turnover or periodic rotation.

The Commissioner agrees that laboratory assistants and animal care personnel need not be identified in the protocol. The list of personnel required to be named is transferred to § 58.185(a)(12).

197. One comment proposed that listing the name of the sponsor and name and address of the testing facility required by § 58.120(a)(3) be restricted to studies done under contract.

The Commissioner does not agree with restricting this requirement to studies done under contract because a testing facility, though a division of the sponsor, may have a specific designation and a location different from the sponsor's, and this information is necessary to determine the exact location of the study.

198. Numerous comments on § 58.120(a)(4) objected to specifying starting and completion dates in the protocol because changing priorities may make such specification impractical. Another comment proposed deletion of the requirement for dates as not relevant to a protocol.

Changing priorities may cause changes in starting dates. For this reason the requirement calls for the proposed dates. If the actual dates differ from the proposed dates, the change should be reflected in a protocol amendment. The dates may be needed in the reconstruction of the study.

199. Ten comments on proposed § 3e.120(a)(7) objected that the proposed date for submission of the final study report to management or to the sponsor was not relevant to a protocol, and one requested a definition of the term "completion date."

The Commissioner agrees that the proposed submission date is not relevant, and the provision is deleted.

200. Numerous comments on § 58.120(a)(6) suggested requiring age of the test system only where applicable or substituting age range for age. Several objected to the requirement for justification for selection of the test system as not relevant to protocol requirements. Additional comments proposed that the requirement for justification be limited to nonroutine systems.

The Commission agrees that age of the test system may not always be critical, and § 58.120(a)(6) now requires number, body weight range, sex, source of supply, species, strain and substrain, and age of the test system only "where applicable." The Commissioner does not agree that justification for selection of the test system is not relevant to a protocol or should be limited to nonroutine systems. Such justification is an integral and essential part of every protocol and to emphasize its importance, the Commissioner is establishing a separate paragraph for this requirement, § 58.120(a)(5).

201. Several comments on § 58.120(a)(8) (proposed § 3e.120(a)(10)) objected that the method of randomization was not relevant to the protocol and suggested requiring justification for the selected method only when nonroutine methods are selected; four comments said justification of the method of randomization is unnecessary; and one comment proposed revised language regarding method of randomization.

The Commissioner finds that the method of randomization or other methods of controlling bias are relevant and are essential parts of a protocol, whether the methods used may be described as routine or nonroutine. The suggested revision is adopted in part, and § 58.120(a)(8) now reads: "A description of the experimental design, including the methods for the control of bias."

202. One comment said a description of the diet used in the study (proposed § 3e.120(a)(11), now § 58.120(a)(9)) was unnecessary unless the diet was unusual. The comment further said that the necessity for including solvents and emulsifiers was questionable because these might not be known at the time the protocol is written.

The Commissioner advises that the phrase "and/or identification" in § 58.120(a)(9) permits a commercial animal diet to be identified by its name. The need for using solvents or emulsifiers may not be known when the protocol is written; however, when this information is available and the solvents, etc., are selected, this fact should be reflected in a protocol amendment.

203. Nine comments pointed out that the degree of absorption (proposed § 3e.120(a)(14)), now § 58.120(a)(12)) is usually unknown at the time of the preparation of the protocol.

The Commissioner recognizes that absorption studies may be conducted concurrently with or as part of the nonclinical laboratory study and points out that the requirements of § 58.120(a)(12) can be fulfilled by amending the protocol.

204. Nine comments suggested deletion of the requirement that the protocol include the records to be maintained (proposed § 3e.120(a)(16), now § 58.120(a)(14)) because this duplicates the requirements under another provision of the regulation.

The Commissioner concludes that the protocol should include a plan identifying the records to be maintained and, therefore, does not agree that § 58.120(a)(14) should be deleted.

CONDUCT OF A NONCLINICAL LABORATORY STUDY

205. Several comments objected to the § 58.130(c) requirement that specimens be identified. Three comments proposed revisions to eliminate the list of specific items (test system, study, nature, date of collection) included for identification of specimens. Numerous comments objected to the identification system as overly restrictive, stating that a coding system should be permitted.

The Commissioner rejects the suggested modifications because the requirements are designed to preclude error. The specific items required to identify a specimen are the minimum necessary to prevent mixup of specimens and permit orderly storage. The Commissioner does not agree that this system is overly restrictive because it does not preclude a coding system.

206. Numerous comments objected to the requirement, in § 58.130(e), for recording data in bound books with prenumbered pages as costly, time-consuming, overly restrictive, and difficult for long-term studies. Six were concerned that much information is too voluminous to be recorded directly and that reference to other documents should be permitted to justify changes, and two comments objected to recording "dictated observations" in ink.

The Commissioner agrees that the requirement for bound books is too restrictive in view of both the variety of data recording procedures that can be used in nonclinical laboratory studies covered by this part and the many ways in which data are generated and collected for these studies. He is, therefore, revising the section. As revised, § 58.130(e) does not preclude reference to other documents if the documents are clearly identified and available. The requirements of the section can be met by maintaining the dictation media or an exact transcription.

207. Three comments proposed that § 58.103(e) be revised to reflect the

three types of computer entries, i.e., direct on-line recording, input from computer readable forms, and input transcribed from recorded raw data. An additional comment suggested revised language to achieve this purpose; and two comments stated that computer printouts of interim display data need not be maintained when the data are wholly contained in subsequent iterations.

The revised wording of § 58.130(e) is equally applicable to the various forms of computer data entries. The Commissioner advises that where the data for computer input are in machine-readable form, such as marketed-sense cards, or are transcribed from recorded raw data, the machine-readable forms or the recorded raw data would constitute raw data within the definition of this part. Where input is via direct on-line recording, the magnetic media and the program would constitute raw data within the meaning of this part.

208. Three comments objected that a daily signature and date for each entry would be burdensome in studies involving daily measurements on each animal.

Section 58.130(e) does not require signing and dating of every individual item recorded. An entry can consist of several observations of several animals made by the same person.

209. Three comments suggested deletion of proposed § 3e.130(f), which required the review of all recorded data, because this duplicated the function of the study director.

The Commissioner agrees that these requirements are adequately addressed by § 58.33(b), and the paragraph is deleted.

RECORDS AND REPORTS

REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

210. Seven comments said the requirement that the final report include all raw data and calculations proposed in § 3e.185(a)(3) is not practical and that a recapitulation should be adequate.

The Commissioner agrees, and the requirement that all raw data be included in the final report is deleted.

211. Two comments on § 58.185(a)(3) stated that the scope of the term "method" was not clear.

The Commissioner advises that "method" does not mean that either the actual calculations or a step-by-step reiteration of the process be included. The name of the method, the description of the method, or a reference to an article or test describing the method will be sufficient.

212. Several comments on § 58.185(a)(4) stated that the final report should provide only a reference to the information on "strength, quality, and purity" rather than the actual values for those characteristics.

The Commissioner does not agree. The final report should include actual values for all characteristics required for proper identification. Because the actual values for strength, quality, and purity are not, in every case, sufficient for adequate identification, the word "quality" has been stricken and the words "and composition or other appropriate characteristics" have been added. The additional language will permit the use of any characteristic which facilitates identification of the test and control article.

213a. Several comments on § 58.185(a)(5) stated that the requirement that stability of the test and control articles be described should be narrowed.

The Commissioner finds that stability information must be submitted as part of the final report. The extent of stability testing required by these regulations is discussed at paragraphs 176, 185, 186, and 189 above.

b. Comments on proposed § 3e.185(a)(8) (now § 58.185(a)(7)) requested that the words "appropriate and necessary" be inserted following the words "procedure used", for identifying the test system.

The Commissioner is modifying § 58.185(a)(7) to require reporting such details where applicable.

214. Seven comments on § 58.185(a)(12) protested the requirement that the final report include reports of each of the individual scientists or other professionals involved in the study.

The Commissioner concludes that the individual reports are required to assure that the final results reported accurately reflect the findings of the individual scientists.

215. A number of comments on § 58.185(a)(3) objected to reporting the location of the raw data in the final report.

For the purpose of information retrieval, the Commissioner is of the opinion that the location of the raw data should be specified.

216. The Commissioner advises that the list of personnel required to be named in the final report as specified in § 58.185(a)(12) has been broadened to include all professionals. (See paragraph 196 above.)

STORAGE AND RETRIEVAL OF RECORDS AND DATA

217. Several comments requested revision and clarification of "other information" in § 58.190(a).

The phrase "and other information" is deleted because it is subsumed by the specific requirements for documentation.

218. Five comments requested clarification of the term "specimen" as used in § 58.190(b).

The term "specimen" is defined in § 58.3(j) and means any material derived from a test system for examination or analysis. This includes wet specimens, histological blocks, and slides that yield information pertinent to the outcome of the study. Such specimens are required to bear sufficient labeling to permit identification and expedient retrieval.

219. Several comments stated that the prohibition against "intermingling" of specimens was unnecessary if specimens are properly labeled and indexed.

The Commissioner agrees and finds that the storage requirements are adequate to achieve their purpose without any further prohibitions. The reference to intermingling of samples is, therefore, deleted.

220. Seven comments said proposed § 3e.190(c) was unclear or redundant and required the maintenance of unnecessary duplicative files by both the testing facility and the sponsor.

The Commissioner agrees with the comments, and the paragraph is deleted.

221. A number of comments requested that § 58.190(c) provide that more than one person be permitted to be responsible for the archives.

The Commissioner reaffirms the need for one individual to be accountable for the maintenance and security of the archives to prevent access by unauthorized personnel. Such access could lead to the loss of, or damage to, records and specimens required to be maintained by these regulations. This provision does not preclude delegation of duties to other individuals who may help maintain the archives.

222. Comments on § 58.190(e) suggested that coding of archival contents should be allowed and objected that the section would require four-way indexing.

The paragraph is revised for clarity. As revised, the use of a coding system is permitted; however, the cross-reference indexing system is retained as a requirement.

223. Section 58.190(g) is deleted because the inspection requirements are adequately addressed by § 58.15.

RETENTION OF RECORDS

224. Several comments stated that the proposed record retention requirements were inconsistent with those previously established.

A new paragraph (a) is added to § 58.195 to make it clear that the record retention requirements of this section do not supersede those of any other regulations in this chapter.

225. Several comments pointed out that IND's are not "approved" and

asked that the record retention requirements for IND's be clarified.

The Commissioner agrees that the record retention requirements, as they apply to both IND's and IDE's, need clarification. In addition to the fact that IND's are not, in a technical sense, "approved," the Commissioner has considered the fact that when either an IND or an IDE is submitted to the agency, the application may contain voluminous data collected over a number of years. It was not the intent of these regulations that such supporting IND or IDE data be destroyed after 2 years because not all studies submitted at the time of filing may be of interest to the agency until several years after submission. Therefore, a new sentence is added to § 58.195(b)(1), which states that the 2-year retention requirement does not apply to studies supporting notices of claimed investigational exemptions for new drugs (IND's) or applications for investigational device exemptions (IDE's). These records are governed by § 58.195(b)(2) and shall be retained for at least 5 years. This additional language clarifies both agency policy and current scientific practice which is, in most cases, to maintain such study records far longer than 5 years.

226. One comment said the variable record retention periods are unworkable, and another said records should be maintained as long as the public is exposed to a chemical.

The record retention period represents the minimum deemed appropriate. For uniformity, all records may be retained for 5 years. Longer retention periods are unnecessary because each nonclinical testing facility will be inspected every 2 years. Studies conducted at facilities that are in substantial compliance with these regulations will be presumed to be valid. When significant deviations are discovered, steps will be taken to validate individual studies before the record retention period expires.

227. Twenty-three comments on § 58.195(b)(3) objected to the record retention requirement as it applies to terminated or discontinued studies, stating that the requirement goes beyond the intent expressed in the definitions or that FDA lacks the authority to require that such studies be retained.

The Commissioner finds that such studies are frequently capable of yielding information applicable to evaluations of related compounds. In the interest of the public health, all such data derived from studies originally intended to be submitted to the agency should be available to the agency. This is particularly important when studies are terminated because of preliminary findings that the test article causes adverse effects at such low levels that any safe use of the article is precluded. The general question of FDA's authority is discussed in paragraph 5 above.

228. With respect to retention of appropriate samples, including wet specimens, several comments on § 58.195(c) requested that the regulations specifically set forth conditions of storage. Others felt that this requirement would be of doubtful value, and several were concerned that the retention period not exceed that which could adversely affect sample integrity.

The Commissioner states that it would be impractical to attempt to specify the specific storage conditions for sample retention. This should be left to the judgment of the testing facility. It is essential as a check on recorded observations that, wherever possible, samples be retained for confirmation of findings. Such samples should be retained for the minimum period specified in the regulations. The regulation clearly states that fragile samples shall be retained only so long as the quality of the preparation affords evaluation.

229. Three comments on § 58.195(e) objected to archive retention of curricula vitae and job descriptions of all personnel involved in the study.

Section 58.195(e) is revised to permit this information to be retained as part of the testing facility employment records.

230. One comment on § 58.195(f) stated that equipment records should be maintained in an independent log rather than maintained as part of each study.

The Commissioner advises that the language of the section does not preclude such an approach. Records of maintenance and calibration of equipment may be kept in a repair manual or on a tag affixed to the instrument. The reference to cleaning records is deleted.

Disqualification of Testing Facilities

PURPOSE

231. Many comments were received concerning the general concept and purpose of disqualification.

The Commissioner believes that many of these comments were based, at least in part, on misunderstanding of the frequency with which disqualification might be used. The Commissioner believes disqualification is an important alternative to rejection of specific studies and legal prosecution because it can reduce by consolidation the number of FDA investigations and administrative proceedings that might be required if FDA acted only on a study-by-study basis. To clarify the agency's intent regarding the disqualification mechanism and to allay fears that this sanction might be abused, the Commissioner is revising Subpart K of the regulations to define more clearly the grounds for disqualification.

231. Section 58.200(a) has been revised to clarify the purposes of disqualification. The first purpose stated in the section is to permit FDA to exclude from consideration any completed studies conducted by a testing facility which has failed to comply with good laboratory practice requirements until it can adequately be demonstrated that the noncompliance did not occur during, or did not affect the validity of data generated by, a particular study. Thus, for studies completed before disqualification, the order of disqualification creates a rebuttable presumption that all studies previously conducted by the facility are unacceptable. Such a study may be accepted, however, upon presentation of evidence demonstrating that the noncompliance which resulted in the disqualification did not affect the particular study. The second purpose set forth in the revision of § 58.200(a) is to exclude studies completed after the date of disqualification from consideration until the facility can satisfy the Commissioner that it will conduct studies in compliance with the regulations. (See also the discussion in paragraph 241.)

GROUNDS FOR DISQUALIFICATION

232. Many comments argued that the disqualification provisions appeared to be overly harsh, arbitrary, and ambiguous.

To clarify the agency's intent, the Commissioner is revising the section. The primary function of the agency's regulation of nonclinical laboratory testing is to assure the quality and integrity of data used in making judgments about the safety of products regulated by the agency. The grounds for disqualification are based on those types of noncompliance that significantly impair achievement of those objectives. Proposed § 3e.202(a) through (p) is deleted, and new § 58.202(a) through (c) clarifies the policy that a testing facility may be disqualified only if the Commissioner finds all three of the following: (1) That the testing facility failed to comply with one or more of the standards set forth in Part 58 or in any other FDA regulations regarding standards for nonclinical testing facilities (e.g., any supplemental requirements in the IND or IDE regulations); (2) that the noncompliance adversely affected the validity of the data produced by the study; and (3) that other lesser regulatory actions, such as warnings or rejection of data from individual nonclinical laboratory studies, have not been or probably will not be adequate to achieve compliance. This

approach will assure that the sanction will not be used in trivial situations, but will be invoked only when the violation has compromised the integrity of a study. It further requires the Commissioner to consider the availability and probable effectiveness of lesser sanctions as an alternative to disqualification. It would not, however, preclude disqualification without prior warning.

As pointed out in the preamble to the proposed regulations, the provisions for disqualification are not to be interpreted as either the exclusive or primary administrative action for noncompliance with good laboratory practice. Disqualification is designed to provide FDA with an enforcement tool that is more efficient and effective than a study-by-study review when it becomes apparent that a testing facility is not capable of producing accurate and valid test results. The disqualification of a nonclinical testing facility will be reserved for the the rare case when the rejection of a particular study is an inadequate regulatory response. The testing facility and/or the sponsor of the nonclinical laboratory study may also be prosecuted for violations of Federal criminal laws, including section 301(e) of the Federal Food, Drug, and Cosmetic Act (failure to make a report required under certain other sections of the act, because a grossly erroneous or inadequate report does not fulfill the statutory obligation) and 18 U.S.C. 1001 (submission of a false report to the government). Even where the testing facility is not under a direct statutory obligation to submit information to FDA, and in fact does not send data to the agency but merely transmits them to the sponsor, the facility is likely to be aware that FDA will be the ultimate recipient. In such cases, it may be liable for aiding and abetting in the violation (18 U.S.C. 2) or for causing the violation to be made by a third party.

233. Two comments stated that the disqualification regulation seemed to apply only to private firms.

This interpretation is incorrect. The preamble to the proposed regulations makes clear the policy that the good laboratory practice regulations are to apply to any institution that generates or otherwise prepares safety data for submission to FDA. Included in that definition, to the extent that they prepare safety data to be submitted to FDA in support of petitions for regulated products, are, for example, veterinary and medical clinics, universities and State experimental stations, and State and Federal Government research laboratories. Accordingly, disqualification provisions apply equally to all facilities that prepare safety data for submission to FDA. The language regarding the intended use of sanctions is incorporated into § 58.202(c).

NOTICE OF AND OPPORTUNITY FOR HEARING ON PROPOSED DISQUALIFICATION

234. Several comments stated that the disqualification process, as proposed, would violate due process, deny a formal hearing, and deny a right of appeal to the courts.

The Commissioner advises, and the revisions to § 58.202 make clear, that the disqualification procedure will not be invoked for minor violations of the regulation. In addition, § 58.204 provides that a regulatory hearing may be conducted in accordance with 21 CFR Part 16. Such a hearing provides all the safeguards essential to due process. See also the FEDERAL REGISTER of 40 FR 40713 et seq. (preamble to Subpart F of 21 CFR Part 2, recodified as 21 CFR Part 16—Regulatory Hearing Before the Food and Drug Administration; section 201(y) of the act (21 U.S.C. 321(y)) (procedural requirements of an "informal hearing"); *Goldberg* v. *Kelly*, 397 U.S. 254 (1970). Judicial review of final administrative action is provided by the Administrative Procedure Act (5 U.S.C. 701 et seq.). See also § 10.45 *Court Review of final administrative action; exhaustion of administrative remedies* (21 CFR 10.45); and 40 FR 40689-40691 (preamble to procedural regulations, § 2.11 (recodified as 21 CFR 10.45)).

235. Several comments expressed the concern that any regulatory hearing conducted under 21 CFR Part 16 should provide for the confidentiality of all data on which the hearing is based.

The Commissioner advises that § 16.60(a) (21 CFR 16.60(a)) provides adequate safeguards when required to maintain the confidentiality of commercial information.

236. One comment stated that if notice for such a hearing should be mailed to a facility, more than 3 days should be allowed for a facility to be able to prepare itself to come to a meeting.

The Commissioner finds that the provisions of § 16.22 (21 CFR 16.22) provide adequate flexibility for any party responding to a notice of opportunity for a hearing. See also the comments addressed to 21 CFR 52.204, set out in the preamble to the proposed regulations on obligations of sponsors and monitors, published in the FEDERAL REGISTER of September 27, 1977 (42 FR 49619).

237. One comment suggested that § 58.204 include a provision specifying that a sponsor be allowed to intervene in the hearing process when a notice of opportunity for a hearing has issued to a testing facility that is performing studies under contract for the sponsor.

Inasmuch as the disqualification process in such a case is directed at the testing facility rather than the sponsor and inasmuch as the alleged violations involved would be those of the testing facility, the Commissioner finds that intervention by a sponsor (or, in many cases, multiple sponsors) would serve no useful purpose. As noted in the preamble to the proposed regulation (41 FR 51218), a sponsor who wishes to contest a finding that a particular study or studies is or are inadequate will be provided an opportunity to do so by the procedures for denying or withdrawing the approval of an application for a research or marketing permit.

238. Concern was also expressed that a reasonable time be provided to allow a sponsor to conduct a new test prior to termination or withdrawal.

The Commissioner emphasizes that in those cases in which a safety decision has been based on data that have subsequently been called into question, protection of the public requires that proceedings be instituted without delay. As previously noted, opportunity to contest a finding that a particular study is so inadequate that it will not support a claim of safety of a product will be provided by procedures set forth in other regulations, e.g., withdrawal of an NDA.

FINAL ORDER ON DISQUALIFICATION

239. Several comments stated that § 58.206 should provide specifically for appeal to the Federal courts following a final decision to disqualify by the Commissioner.

The Commissioner notes that the provisions of 21 CFR 16.120 and 10.45 adequately address this point. These regulations clearly state the provisions that apply to court review of final administrative action.

240. One comment suggested that § 58.206(b) be modified to require that sponsors be notified, when applicable, at the time of issuance of a final order to a testing facility.

The Commissioner advises that such notification, which is discretionary, is expressly provided for in § 58.213(b). Additionally, § 58.206(a) and (b) are revised to reflect the requirement that the Commissioner must make the findings required by § 58.202 before a final order disqualifying a nonclinical testing facility shall issue.

ACTIONS UPON DISQUALIFICATION

241. Several comments objected to the retroactive provisions of § 58.210(a), which state that once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, that contains or relies upon any nonclinical

laboratory study conducted by the disqualified testing facility may be examined to determine whether these studies were or would be essential to a decision.

The Commissioner advises that calling into question studies performed by a subsequently disqualified testing facility does not represent a departure from prior FDA policy in other areas. FDA must make additional inquiries to establish safety any time a question is raised about data previously submitted, regardless of whether a disqualification procedure exists. Section 58.210(a) allows the person relying on the study in question to establish that the study was not affected by the circumstances that led to disqualification. The safety of the public would not be adequately protected were no such validation required when serious questions are raised regarding the adequacy of data upon which regulatory decisions are based.

Section 58.210 is revised by the addition of paragraph (b), which states that no nonclinical laboratory study begun after a facility has been disqualified will be considered in support of any application for a research or marketing permit unless the facility has been reinstated under § 58.219. This addition makes it clear that, in such a case, no subsequent information can be submitted for purposes of subsequent validation. If the facility is reinstated, however, the study might by acceptable to FDA. This provision does not relieve the applicant from any other requirement under FDA regulations that all data and information regarding clinical experience with the article in question be submitted to the agency.

242. Many comments regarding § 58.210 were based on the assumption that the disqualification process might be invoked for a minor violation of the good laboratory practice regulation and stated that calling studies into question based on a minor violation was unreasonable.

As previously discussed, § 58.202 is revised to make it clear that the disqualification process will be reserved for those situations in which lesser sanctions, e.g., rejection of individual studies, will not suffice. Because disqualification will be reserved for use in serious situations, the Commissioner finds that calling into question all studies done before or after disqualification is warranted.

PUBLIC DISCLOSURE OF INFORMATION UPON DISQUALIFICATION

243. Several comments said that proprietary or trade secret documents should not be released. Others urged that disqualification records not be disclosed.

The Commissioner advises that release of all such documents is governed by the provisions of the Freedom of Information Act (5 U.S.C. 552) and 21 CFR Part 20 and need not be separately dealt with in this regulation. Interested parties are referred specifically to Part 20—Public Information (21 CFR Part 20). Section 20.61 (21 CFR 20.61) deals with trade secrets and commercial information and § 20.64 (21 CFR 20.64) deals with investigatory records. The preamble to the public information regulations (39 FR 44602 et seq.) (since recodified as Part 20) discusses these issues at length.

244. One comment on § 58.213 stated that no notification of other government departments or agencies should issue until completion of the judicial process.

The Commissioner disagrees and finds that withholding notification until completion of the administrative process by the agency provides an adequate opportunity for a testing facility to be heard prior to the issuance of any such notification.

245. Another comment stated that because FDA is a Federal agency, notification of State agencies is outside FDA's jurisdiction.

The Commissioner points out that section 705(b) of the act (21 U.S.C. 375(b)) provides for dissemination of information regarding food, drugs, or devices in situations involving imminent danger to health or gross deception of the consumer. In addition, the Commissioner emphasizes that he proposes to notify the States only in those situations for which adequate cause has been established and for which a final order has been issued. Section 58.213(a) is amended to make it clear that such notification shall state that it is given because of the relationship between the testing facility and the person notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified. Additionally, § 58.213 is modified to make it clear that notification of disqualification may be sent by the Commissioner not only to other Federal agencies but to any other person known to have professional relations with the disqualified testing facility. This includes sponsors of studies being performed by the facility.

246. A comment suggested that the scope of notification should be limited to those nonclinical laboratory studies upon which the decision to disqualify was based.

The language of § 58.213 makes it clear that notification may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations. The Commissioner finds that, given the expressed purpose of notification, further limitation would be inappropriate.

ALTERNATIVE OR ADDITIONAL ACTIONS TO DISQUALIFICATION

247. One comment on § 58.215 suggested that informal procedures be used prior to the institution of more formal procedures.

The Commissioner notes that this approach was discussed in the preamble to the proposed regulation at 41 FR 51218. Because such informal procedures have, in the past, doubled the time and expense of all involved parties without discernible benefit, the Commissioner has decided not to provide for informal procedures in these regulations.

SUSPENSION OR TERMINATION OF A TESTING FACILITY BY A SPONSOR

248. Many comments on § 58.217 said that the section seemed to be an attempt on the part of FDA to provide legal grounds for the unilateral breaking of contracts between private parties.

The Commissioner finds that the section, as written, was subject to a great deal of misunderstanding. Therefore, the section is revised. The Commissioner advises that nothing in Part 58 is intended to infringe upon or alter the private contractual arrangements between a sponsor and a nonclinical testing facility. A sponsor may terminate a testing facility for reasons of its own whether or not FDA has begun any action to disqualify that facility. Where a sponsor has independent grounds for suspending or terminating studies performed for that sponsor by the facility under contract, the fact that FDA has not itself disqualified the facility may not be raised by the contract facility as a defense against the sponsor.

249. Several comments said notification within 5 days was impractical.

The Commissioner agrees, and the time period is extended to 15 working days.

250. A number of comments said the notification requirement provided a sponsor with an unfair opportunity to impugn a contract facility that would have no opportunity for response.

The Commissioner emphasizes that termination of a nonclinical testing facility by a sponsor should be subject to the contract between the two parties. A nonclinical testing facility, as a party to the contract, may protect itself from unjust termination by the terms of its contract with the sponsor. Remedies for both parties to such a contract may be spelled out in the contract and are governed by principles of contract law. The Commissioner fur-

ther emphasizes that the requirement that a sponsor notify FDA when it has terminated or suspended a testing facility applies only to those cases in which an application for a research or marketing permit has been submitted. Where no application has been submitted, no notification is required.

REINSTATEMENT OF A DISQUALIFIED TESTING FACILITY

251. One comment on § 58.219 expressed concern that when read with § 58.210, it was confusing.

The Commissioner finds that the addition of § 58.210(b) substantially clarifies the status of studies conducted before, during, and after disqualification and that further amendment is unnecessary.

252. A typographical error in the last sentence of § 58.219 has been corrected. The last sentence now reads: "A determination that a testing facility has been reinstated is disclosable to the public under Part 20 of this Chapter."

CONFORMING AMENDMENTS

253. The Commissioner is adding to or revising provisions in the regulations regarding food and color additives, new drugs for investigational use, new drug applications, OTC drug products, antibiotic drugs, new animal drug applications, biological product licenses, and performance standards for electronic products to incorporate appropriate implementing provisions for, and cross references to, Part 58, which is being added by this document. Each of the regulations requires the submission of data which may include nonclinical laboratory studies. The regulations are being revised to require, with respect to each nonclinical laboratory study contained as part of the submitted information, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. The revisions highlight the fact that although studies not conducted in compliance with the regulations may continue to be submitted to FDA, the burden of establishing that the noncompliance did not affect the quality of the data submitted is on the person submitting the noncomplying study.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701(a), 706, and 801, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360j, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n)) and under authority delegated to him (21 CFR 5.1), the Commissioner amends Chapter I of 21 CFR as follows:

SUBCHAPTER A—GENERAL

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. Part 16 is amended in § 16.1 by redesignating paragraph (b)(30) as paragraph (c) and by adding new paragraph (b)(30), to read as follows:

§ 16.1 Scope.

* * * * * * *

(b) * * *

(30) Section 58.204(b) of this chapter, relating to disqualifying a nonclinical laboratory testing facility.

(c) Any other provision in the regulations in this chapter under which a party who is adversely affected by regulatory action is entitled to an opportunity for a hearing, and no other procedural provisions in this part are by regulation applicable to such hearing.

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2. Part 58 is added to read as follows:

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Sec.
58.1 Scope.
58.3 Definitions.
58.10 Applicability to studies performed under grants and contracts.
58.15 Inspection of a testing facility.

Subpart B—Organization and Personnel

58.29 Personnel.
58.31 Testing facility management.
58.33 Study director.
58.35 Quality assurance unit.

Subpart C—Facilities

58.41 General.
58.43 Animal care facilities.
58.45 Animal supply facilities.
58.47 Facilities for handling test and control articles.
58.49 Laboratory operation areas.
58.51 Specimen and data storage facilities.
58.53 Administrative and personnel facilities.

Subpart D—Equipment

58.61 Equipment design.
58.63 Maintenance and calibration of equipment.

Subpart E—Testing Facilities Operation

58.81 Standard operating procedures.
58.83 Reagents and solutions.
58.90 Animal care.

Subpart F—Test and Control Articles

58.105 Test and control article characterization.
58.107 Test and control article handling.
58.113 Mixture of article with carriers.

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

58.120 Protocol.
58.130 Conduct of a nonclinical laboratory study.

Subparts H and I—[Reserved]

Subpart J—Records and Reports

58.185 Reporting of nonclinical laboratory study results.
58.190 Storage and retrieval of records and data.
58.195 Retention of records.

Subpart K—Disqualification of Testing Facilities

58.200 Purpose.
58.202 Grounds for disqualification.
58.204 Notice of and opportunity for hearing on proposed disqualification.
58.206 Final order on disqualification.
58.210 Actions upon disqualification.
58.213 Public disclosure of information regarding disqualification.
58.215 Alternative or additional actions to disqualification.
58.217 Suspension or termination of a testing facility by a sponsor.
58.219 Reinstatement of a disqualified testing facility.

AUTHORITY: Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463, as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360j, 371(a), 376, and 381); secs. 215, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n).

Subpart A—General Provisions

§ 58.1 Scope.

This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 706, and 801

of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

§ 58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) "Test article" means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act.

(c) "Control article" means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article other than a test article that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

(d) "Nonclinical laboratory study" means any in vivo or in vitro experiment in which a test article is studied prospectively in a test system under laboratory conditions to determine its safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

(e) "Application for research or marketing permit" includes:

(1) A color additive petition, described in Part 71 of this chapter.

(2) A food additive petition, described in Parts 171 and 571 of this chapter.

(3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.35 of this chapter.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1 of this chapter.

(5) A "Notice of Claimed Investigational Exemption for a New Drug," described in Part 312 of this chapter.

(6) A "new drug application," described in Part 314 of this chapter.

(7) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in Part 330 of this chapter.

(8) Data and information regarding a prescription drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, to be described in this chapter.

(9) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in Part 430 of this chapter.

(10) A "Notice of Claimed Investigational Exemption for a New Animal Drug," described in Part 511 of this chapter.

(11) A "new animal drug application," described in Part 514 of this chapter.

(12) Data and information regarding a drug for animal use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, to be described in this chapter.

(13) An "application for a biological product license," described in Part 601 of this chapter.

(14) An "application for an investigational device exemption," described in Part 812 of this chapter.

(15) An "Application for Premarket Approval of a Medical Device," described in section 515 of the act.

(16) A "Product Development Protocol for a Medical Device," described in section 515 of the act.

(17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in section 513 of the act.

(18) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in section 514 of the act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in Subpart D of Part 1003 of this chapter.

(20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in § 1010.4 of this chapter.

(22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in § 1010.5 of this chapter.

(f) "Sponsor" means:

(1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study;

(2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

(3) A testing facility, if it both initiates and actually conducts the study.

(g) "Testing facility" means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. "Testing facility" includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. "Testing facility" encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

(h) "Person" includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

(i) "Test system" means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. "Test system" also includes appropriate groups or components of the system not treated with the test or control articles.

(j) "Specimen" means any material derived from a test system for examination or analysis.

(k) "Raw data" means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

(l) "Quality assurance unit" means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

(m) "Study director" means the individual responsible for the overall conduct of a nonclinical laboratory study.

(n) "Batch" means a specific quantity or lot of a test or control article that has been characterized according to § 58.105(a).

§ 58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

§ 58.15 Inspection of a testing facility.

(a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.

Subpart B—Organization and Personnel

§ 58.29 Personnel.

(a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

(b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

(c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

(e) Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

(f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

§ 58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

(a) Designate a study director as described in § 58.33, before the study is initiated.

(b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study, and document and maintain such action as raw data.

(c) Assure that there is a quality assurance unit as described in § 58.35.

(d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

(e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

(f) Assure that personnel clearly understand the functions they are to perform.

(g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

§ 58.33 Study director.

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall assure that:

(a) The protocol, including any change, is approved as provided by § 58.120 and is followed.

(b) All experimental data, including observations of unanticipated responses to the test system are accurately recorded and verified.

(c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.

(d) Test systems are as specified in the protocol.

(e) All applicable good laboratory practice regulations are followed.

(f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

§ 58.35 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit composed of one or more individuals who shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(b) The quality assurance unit shall:

(1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, name of the sponsor, name of the study director, and status of the final report.

(2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible.

(3) Inspect each phase of a nonclinical laboratory study periodically and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for re-inspection. For studies lasting more than 6 months, inspections shall be conducted every 3 months. For studies

lasting less than 6 months, inspections shall be conducted at intervals adequate to assure the integrity of the study. Any significant problems which are likely to affect study integrity found during the course of an inspection shall be brought to the attention of the study director and management immediately.

(4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.

(6) Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.

(7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.

(c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration.

(d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.

(e) All records maintained by the quality assurance unit shall be kept in one location at the testing facility.

Subpart C—Facilities

§ 58.41 General.

Each testing facility shall be of suitable size, construction, and location to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

§ 58.43 Animal care facilities.

(a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

(b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(c) Separate areas shall be provided for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

(d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

(e) Animal facilities shall be designed, constructed, and located so as to minimize disturbances that interfere with the study.

§ 58.45 Animal supply facilities.

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Refrigeration shall be provided for perishable supplies or feed.

§ 58.47 Facilities for handling test and control articles.

(a) As necessary to prevent contamination or mixups, there shall be separate areas for:

(1) Receipt and storage of the test and control articles.

(2) Mixing of the test and control articles with a carrier, e.g., feed.

(3) Storage of the test and control article mixtures.

(b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

§ 58.49 Laboratory operation areas.

(a) Separate laboratory space shall be provided, as needed, for the performance of the routine procedures required by nonclinical laboratory studies, including specialized areas for performing activities such as aseptic surgery, intensive care, necropsy, histology, radiography, and handling of biohazardous materials.

(b) Separate space shall be provided for cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study.

§ 58.51 Specimen and data storage facilities.

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

§ 58.53 Administrative and personnel facilities.

(a) There shall be space provided for the administration, supervision, and direction of the testing facility.

(b) Separate space shall be provided for locker, shower, toilet, and washing facilities, as needed.

Subpart D—Equipment

§ 58.61 Equipment design.

Automatic, mechanical, or electronic equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

§ 58.63 Maintenance and calibration of equipment.

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

(b) The written standard operating procedures required under § 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration and/or standardization of equipment, and shall specify remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation, and copies of the standard operating procedures shall be made available to laboratory personnel.

(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on

equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

Subpart E—Testing Facilities Operation

§ 58.81 Standard operating procedures.

(a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

(b) Standard operating procedures shall be established for, but not limited to, the following:

(1) Animal room preparation.

(2) Animal care.

(3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.

(4) Test system observations.

(5) Laboratory tests.

(6) Handling of animals found moribund or dead during study.

(7) Necropsy of animals or postmortem examination of animals.

(8) Collection and identification of specimens.

(9) Histopathology.

(10) Data handling, storage, and retrieval.

(11) Maintenance and calibration of equipment.

(12) Transfer, proper placement, and identification of animals.

(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed, e.g., toxicology, histology, clinical chemistry, hematology, teratology, necropsy. Published literature may be used as a supplement to standard operating procedures.

(d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

§ 58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

§ 58.90 Animal care.

(a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

(b) All newly received animals from outside sources shall be placed in quarantine until their health status has been evaluated. This evaluation shall be in accordance with acceptable veterinary medical practice.

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated. If necessary, these animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment and each date of treatment shall be documented and shall be retained.

(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification (e.g., tattoo, toe clip, color code, ear tag, ear punch, etc.). All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

(e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

(f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

(h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

(i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

Subpart F—Test and Control Articles

§ 58.105 Test and control article characterization.

(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented before the initiation of the study. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor before initiation or a nonclinical laboratory study. If the stability of the test and control articles cannot be determined before initiation of a study, standard operating procedures shall be established and followed to provide for periodic re-analysis of each batch.

(c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

(d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by § 58.195.

§ 58.107 Test and control article handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

(a) There is proper storage.

(b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

(c) Proper identification is maintained throughout the distribution process.

(d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

§ 58.113 Mixtures of articles with carriers.

(a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:

(1) To determine the uniformity of the mixture and to determine, periodi-

cally, the concentration of the test or control article in the mixture.

(2) To determine the stability of the test and control articles in the mixture. If the stability cannot be determined before initiation of the study, standard operating procedures shall be established and followed to provide for periodic re-analysis of the test and control articles in the mixture.

(b) For studies of more than 4 weeks' duration a reserve sample of each test or control carrier article mixture shall be taken and retained for the period of time provided by § 58.195.

(c) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

§ 58.120 Protocol.

(a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain but shall not necessarily be limited to the following information:

(1) A descriptive title and statement of the purpose of the study.

(2) Identification of the test and control articles by name, chemical abstract number or code number.

(3) The name of the sponsor and the name and address of the testing facility at which the study is being conducted.

(4) The proposed starting and completion dates.

(5) Justification for selection of the test system.

(6) Where applicable, the number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

(7) The procedure for identification of the test system.

(8) A description of the experimental design, including the methods for the control of bias.

(9) A description and/or identification of the diet used in the study as well as solvents, emulsifiers and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(10) The route of administration and the reason for its choice.

(11) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.

(12) Method by which the degree of absorption of the test and control articles by the test system will be determined if necessary to achieve the objectives of the study.

(13) The type and frequency of tests, analyses, and measurements to be made.

(14) The records to be maintained.

(15) The date of approval of the protocol by the sponsor and the signature of the study director.

(16) A statement of the proposed statistical methods to be used.

(b) All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the study director, dated, and maintained with the protocol.

§ 58.130 Conduct of a nonclinical laboratory study.

(a) The nonclinical laboratory study shall be conducted in accordance with the protocol.

(b) The test systems shall be monitored in conformity with the protocol.

(c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

(d) Records of gross findings for a specimen from postmortem observations shall be available to a pathologist when examining that specimen histopathologically.

(e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated as direct computer input, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In computer driven data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in computer entries shall be made so as not to obscure the original entry, shall indicate the reason for change, and shall be dated and the responsible individual shall be identified.

Subparts H-I—[Reserved]

Subpart J—Records and Reports

§ 58.185 Reporting of nonclinical laboratory study results.

(a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following:

(1) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.

(3) Statistical methods employed for analyzing the data.

(4) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.

(5) Stability of the test and control articles under the conditions of administration.

(6) A description of the methods used.

(7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.

(8) A description of the dosage, dosage regimen, route of administration, and duration.

(9) A description of all circumstances that may have affected the quality or integrity of the data.

(10) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.

(11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

(12) The signed and dated reports of each of the individual scientists or other professionals involved in the study.

(13) The locations where all specimens, raw data, and the final report are to be stored.

(14) The statement prepared and signed by the quality assurance unit as described in § 58.35(b)(7).

(b) The final report shall be signed by the study director.

(c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reason for the correction or addition.

shall be signed and dated by the person responsible.

§ 58.190 Storage and retrieval of records and data.

(a) All raw data, documentation, protocols, specimens, and final reports generated as a result of a nonclinical laboratory study shall be retained.

(b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations.

(c) An individual shall be identified as responsible for the archives.

(d) Only authorized personnel shall enter the archives.

(e) Material retained or referred to in the archives shall be indexed by test article, date of study, test system, and nature of study.

§ 58.195 Retention of records.

(a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter.

(b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting notices of claimed investigational exemption for new drugs (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b)(2) of this section.

(2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

(3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

(c) Wet specimens, samples of test or control articles, samples of test or control article carrier mixtures and specially prepared material (e.g., histochemical, electron microscopic, blood mounts, teratological preparation, and uteri from dominant lethal mutagenesis tests), which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.

(d) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by § 58.35(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.

(e) Summaries of training and experience and job descriptions required to be maintained by § 58.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section.

(f) Records and reports of the maintenance and calibration and inspection of equipment, as required by § 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.

(g) If a facility conducting nonclinical testing goes out of business, all raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The Food and Drug Administration shall be notified in writing of such a transfer.

Subpart K—Disqualification of Testing Facilities

§ 58.200 Purpose.

(a) The purposes of disqualification are: (1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and (2) to exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

(b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

§ 58.202 Grounds for disqualification.

The Commissioner may disqualify a testing facility upon finding all of the following:

(a) The testing facility failed to comply with one or more of the regulations set forth in this part (or any other regulations regarding such facilities in this chapter);

(b) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and

(c) Other lesser regulatory actions (e.g., warnings or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the good laboratory practice regulations.

§ 58.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under § 58.202 which in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.

(b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in Part 16 of this chapter.

§ 58.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaulation of the administrative record of the disqualification proceeding, makes the findings required in § 58.202, he shall issue a final order disqualifying the facility. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the testing facility of the action.

(b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in § 58.202, he shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination. Upon issuing a final order the Commissioner shall notify the testing facility and provide a copy of the order.

§ 58.210 Actions upon disqualification.

(a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data such be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

(b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit, unless the facility has been reinstated under § 58.219. The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

§ 58.213 Public disclosure of information regarding disqualification.

(a) Upon issuance of a final order disqualifying a testing facility under § 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations set forth in this part. Such notice, if given, shall include a copy of the final order issued under § 58.206(a) and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified.

(b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under Part 20 of this chapter.

§ 58.215 Alternative or additional actions to disqualification.

(a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

(b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.

§ 58.217 Suspension or termination of a testing facility by a sponsor.

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Bureau of the Food and Drug Administration (whether approved or not), it shall notify that Bureau in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit the results of th study to the Food and Drug Admini tration.

§ 58.219 Reinstatement of a disqu testing facility.

A testing facility that has been di qualified may be reinstated as an a ceptable source of nonclinical labor tory studies to be submitted to th Food and Drug Administration if th Commissioner determines, upon evaluation of the submission of th testing facility, that the facility ca adequately assure that it will condu future nonclinical laboratory studi in compliance with the good labor tory practice regulations set forth this part and, if any studies are cu rently being conducted, that the qua ity and integrity of such studies ha not been seriously compromised. A di qualified testing facility that wishes be so reinstated shall present in wr ing to the Commissioner reasons wh it believes it should be reinstated a a detailed description of the correcti actions it has taken or intends to ta to assure that the acts or omissio which led to its disqualification w not recur. The Commissioner may co dition reinstatement upon the testi facility being found in complian with the good laboratory practice re ulations upon an inspection. If a te ing facility is reinstated, the Comm sioner shall so notify the testing ty and all organizations and p who were notified, under § 58.21 the disqualification of the testing cility. A determination that a testi facility has been reinstated is disclo ble to the public under Part 20 of th chapter.

PART 71—COLOR ADDITIVE PETITIONS

3. Part 71 is amended:

a. § 71.1 by adding new paragra (g), to read as follows:

§ 71.1 Petitions.

* * * * *

(g) If nonclinical laboratory stud are involved, petitions filed with t Commissioner under section 706(b) the act shall include with respect each nonclinical study contained the petition, either a statement th the study was conducted in compliar with the good laboratory practice r ulations set forth in Part 58 of t chapter, or, if the study was not co ducted in compliance with such re lations, a statement that describes detail all differences between the pr tices used in the study and those quired in the regulations.

b. In § 71.6(b) by adding a new sentence at the end of the paragraph to read as follows:

§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.

• • • • •

(b) • • •. If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical laboratory study contained in the petition, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

Subchapter B—Food for Human Consumption

PART 170—FOOD ADDITIVES

4. Part 170 is amended:

a. In § 170.17 by adding new paragraph (c), to read as follows:

§ 170.17 Exemption for investigational use and procedure for obtaining authorization to market edible products from experimental animals.

• • • • •

(c) If intended for nonclinical laboratory studies in food-producing animals, the study is conducted in compliance with the regulations set forth in Part 58 of this chapter.

• • • • •

b. In § 170.35 by adding new paragraph (c)(1)(vi) to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

• • • • •

(c) • • •

(1) • • •

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

PART 171—FOOD ADDITIVE PETITIONS

5. Part 171 is amended:

a. In § 171.1 by adding new paragraph (k) to read as follows:

§ 171.1 Petitions.

• • • • •

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each nonclinical study contained in the petition, either a statement that the study has been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if any such study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and the good laboratory practice regulations.

b. By revising § 171.6 to read as follows:

§ 171.6 Amendment of petition.

After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amount to a substantive amendment, the petition as amended will be given a new filing date, and the time limitation will begin to run anew. Where the substantive amendment proposes a substantial change to any petition that may affect the quality of the human environment, the petitioner is required to submit an environmental analysis report pursuant to § 25.1 of this chapter. If nonclincial laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY

6. Part 180 is amended in § 180.1 by adding new paragraph (c)(4) to read as follows:

§ 180.1 General.

• • • • •

(c) • • •

(4) If nonclinical laboratory studies are involved, studies filed with the Commissioner shall include, with respect to each study, either a statement that the study has been or will be conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if any such study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and the good laboratory practice regulations.

• • • • •

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

7. In § 312.1 by adding new item 16 to Form FD-1571 in paragraph (a)(2) and by redesignating paragraph (d)(11) as (d)(12) and adding a new paragraph (d)(11), to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) • • •

(2) • • •

Form FD-1571 • • •

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

• • • • •

(d) • • •

(11) All nonclinical laboratory studies were not conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies were not conducted in compliance with such regulations, all differences between the practices used in conducting the study and the good laboratory practice

regulations were not described in detail; or

* * * * *

PART 314—NEW DRUG APPLICATIONS

8. Part 314 is amended:

a. In § 314.1 by adding new item 16 to Form FD-365H in paragraph (c)(2), by redesignating paragraph (f)(7) as (f)(8) and by adding a new paragraph (f)(7) to read as follows:

§ 314.1 Applications.

* * * * *

(c) * * *

(2) * * *

Form FD-356H-Rev. 1974 * * *

16. *Nonclinical laboratory studies.* With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

* * * * *

(f) * * *

(7) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

* * * * *

b. In § 314.8 by adding new paragraph (l) to read as follows:

§ 314.8 Supplemental applications.

* * * * *

(l) A supplemental application that contains nonclinical laboratory studies shall include, with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

c. In § 314.9 by adding paragraph (c) to read as follows:

§ 314.9 Insufficient information in application.

* * * * *

(c) The information contained in an application shall be considered insufficient to determine whether a drug is safe and effective for use unless the application includes, with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

d. In § 314.12 by adding new paragraph (c) to read as follows:

§ 314.12 Untrue statements in application.

* * * * *

(c) All nonclinical laboratory studies contained in the application were not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

e. In § 314.110 by adding new paragraph (a)(9) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(9) The applicant fails to include in the application, with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

* * * * *

f. In § 314.111 by striking the period at the end of paragraph (a)(8), adding in lieu thereof a semicolon and the word "or" and adding new paragraph (a)(9) to read as follows:

§ 314.111 Refusal to approve the application.

(a) * * *

(9) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if such study was not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

g. In § 314.115 by adding new paragraph (c)(6) to read as follows:

§ 314.115 Withdrawal of approval of an application.

* * * * *

(c) * * *

(6) That any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or any differences between the practices used in conducting the study and those required in the regulations were not described in detail.

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND NOT MISBRANDED

9. Part 330 is amended in § 330.10 by adding new paragraph (c) to read as follows:

§ 330.10 Procedures for classifying drugs as generally recognized as and effective and not misbranded, a... for establishing monographs.

* * * * *

(c) Information and data submitted under this section shall include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

PART 430—ANTIBIOTIC DRUGS; GENERAL

10. In § 430.20 by adding new paragraph (e) to read as follows:

§ 430.20 Procedure for the issuance amendment, or repeal of regulations.

* * * * *

(e) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amende

unless each nonclinical laboratory study on which the issuance or amendment of the regulation is based was conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if any such study has not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

11. In § 431.17 by adding new paragraph (j) to read as follows:

§ 431.17 New antibiotic and antibiotic-containing products.

• • • • •

(j) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

Subchapter E—Animal Drugs, Feeds, and Related Products

PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

12. Part 511 is amended in § 511.1 by revising paragraph (b)(4)(ii), to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

• • • • •

(b) • • •

(4) • • •

(ii) All labeling and other pertinent information to be supplied to the investigators. When such pertinent information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

PART 514—NEW ANIMAL DRUG APPLICATIONS

13. Part 514 is amended:

a. In § 514.1 by adding new paragraph (b)(12)(iii) to read as follows:

§ 514.1 Applications.

• • • • •

(b) • • •

(12) • • •

(iii) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

b. In § 514.8 by adding new paragraph (l) to read as follows:

§ 514.8 Supplemental new animal drug applications.

• • • • •

(l) A supplemental application that contains nonclinical laboratory studies shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

c. In § 514.15 by adding new paragraph (c) to read as follows:

§ 514.15 Untrue statements in applications.

• • • • •

(c) Any nonclinical laboratory study contained in the application was conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, and differences between the practices used in the conduct of the study and those required in the regulations were not described in detail.

d. In § 514.110 by adding new paragraph (b)(8) to read as follows:

§ 514.110 Reasons for refusing to file applications.

• • • • •

(b) • • •

(8) It fails to include, with respect to each nonclinical study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

e. In § 514.111 by adding new paragraph (a)(11) to read as follows:

§ 514.111 Refusal to approve an application.

(a) • • •

(11) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or any differences between the practices used in conducting the study and those required in the regulations were not described in detail.

• • • • •

f. In § 514.115 by adding new paragraph (b)(4) to read as follows:

§ 514.115 Withdrawal of approval of applications.

• • • • •

(b) • • •

(4) That any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, and differences between the practices used in conducting the study and the regulations were not described in detail.

• • • • •

PART 570—FOOD ADDITIVES

14. Part 570 is amended:

a. In § 570.17 by adding new paragraph (c) to read as follows:

§ 570.17 Exemption for investigational use and procedure for obtaining authorization to market edible products from experimental animals.

• • • • •

(c) If intended for nonclinical laboratory studies in food-producing animals, the study is conducted in compliance with the regulations set forth in Part 58 of this chapter.

b. In § 570.35 by adding new paragraph (c)(1)(vi) to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

• • • • •

(c) • • •
(1) • • •

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

PART 571—FOOD ADDITIVE PETITIONS

15. Part 571 is amended:

a. In § 571.1 by adding paragraph (k) to read as follows:

§ 571.1 Petitions.

• • • • •

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

b. In § 571.6 by adding the following sentence to the end of the section to read as follows:

§ 571.6 Amendment of petition.

• • • If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each such study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

SUBCHAPTER F—BIOLOGICS

PART 601—LICENSING

16. Part 601 is amended:

a. In § 601.2 by revising paragraph (a) to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

• • • • •

b. By revising § 601.30 to read as follows:

§ 601.30 Licenses required; products for controlled investigation only.

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products that are not imported for sale, barter or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and the requirements set forth in Parts 58 and 312 of this chapter.

SUBCHAPTER J—RADIOLOGICAL HEAL

PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

17. Part 1003 is amended in § 1003.3 by revising paragraph (b), to read a follows:

§ 1003.31 Granting the exemption.

• • • • •

(b) Such views and evidence shall b confined to matters relevant to whetl er the defect in the product or its fai ure to comply with an applicable Fec eral standard is such as to create a sig nificant risk of injury, including gene ic injury, to any person and shall b presented in writing unless the Secr tary determines that an oral presenta tion is desirable. Where such evidenc includes nonclinical laboratory stuc ies, the data submitted shall includ with respect to each nonclinical stud either a statement that each stud was conducted in compliance with th requirements set forth in Part 58 c this chapter, or, if the study was nc conducted in compliance with suc regulations, a statement that describ in detail all differences between th practices used in the study and thos required in the regulations.

• • • • •

PART 1010—PERFORMANCE STANI ARDS FOR ELECTRONIC PRODUCT GENERAL

18. Part 1010 is amended:

a. In § 1010.4 by adding new par graph (b)(1)(ix) to read as follows:

§ 1010.4 Variances.

• • • • •

(b) • • •
(1) • • •

(ix) With respect to each nonclinic study contained in the applicatio either a statement that the study w conducted in compliance with th good laboratory practice regulatio set forth in Part 58 of this chapter, c if the study was not conducted in cor pliance with such regulations, a stat ment that describes in detail all diffe ences between the practices used the study and those required in th regulations.

• • • • •

b. In § 1010.5 by revising paragra (c)(12) to read as follows:

§ 1010.5 Exemptions for products intended for United States Government use.

• • • • •

(c) • • •

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that each study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations.

• • • • •

Effective date. This rule is effective June 20, 1979.

(Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 601, 701(a), 706, and 801, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360i); secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended; 42 U.S.C. 216, 262, 263b-263n).

Dated: December 4, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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